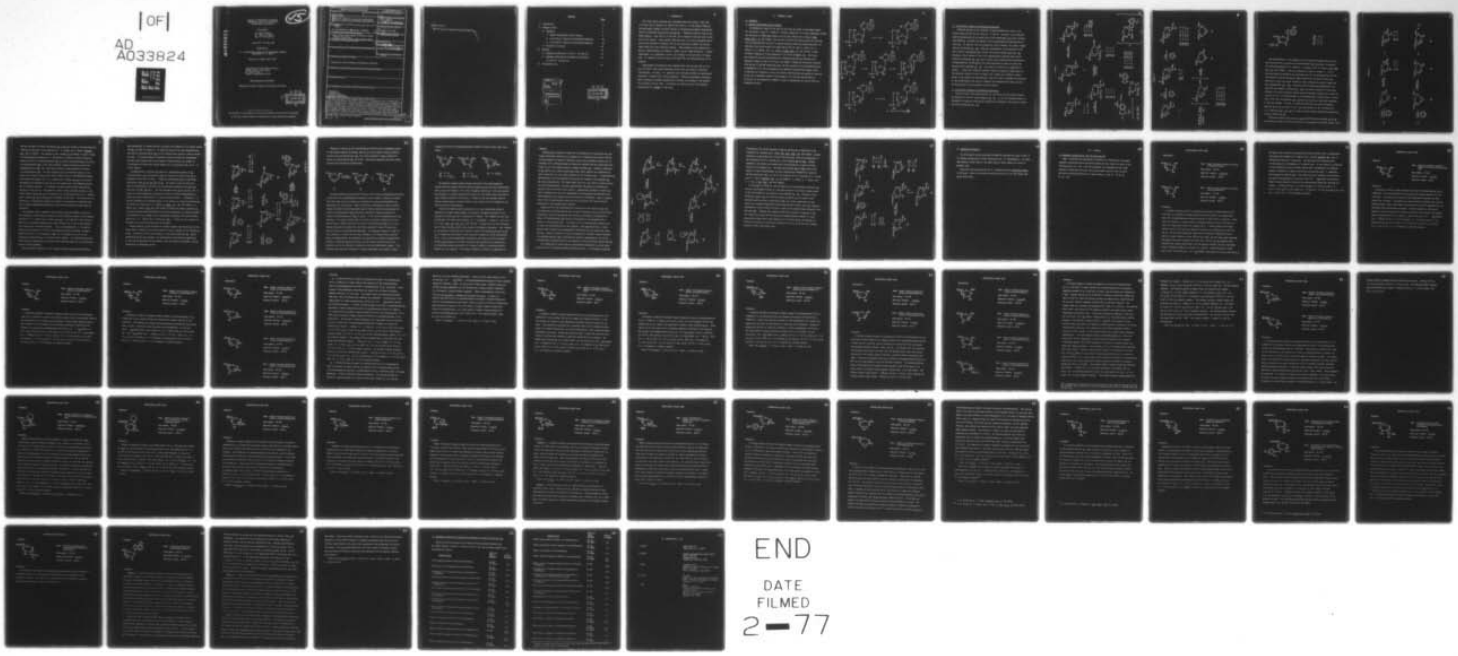
AD-A033 824 SIDNEY FARBER CANCER CENTER BOSTON MASS LABS OF BIOOR--ETC F/G 6/15
ANALOGS OF CORDYCEPTIN AND ADENINE ARABINOSIDE (ARA-A) AS POTEN--ETC(U)
AUG 76 A ROSOWSKY, E J MODEST DAMD17-74-C-4105

UNCLASSIFIED NL

| OF |
AD
A033824



END

DATE
FILMED
2-77

ANALOGS OF CORDYCEPIN AND ADENINE ARABINOSIDE (ARA-A) AS POTENTIAL ANTIMALARIAL NUCLEOSIDES

Final Report

Dr. Andre Rosowsky
Dr. Edward J. Modest
Tel. No. 617-732-3117

1 June 1974 - 30 June 1976

Supported by

U. S. Army Medical Research and Development Command
Washington, D. C. 20315

Contract No. DAMD-17-74-C-4105

Laboratories of BioOrganic Chemistry
Sidney Farber Cancer Center
44 Binney Street
Boston, Massachusetts 02115

DDC AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: Final Report
2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle): ANALOGS OF CORDYCEPIN AND ADENINE ARABINOSIDE (ARA-A) AS POTENTIAL ANTIMALARIAL NUCLEOSIDES
5. TYPE OF REPORT & PERIOD COVERED: Final Report, 1 June 74 - 30 June 76
6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): Drs. Andre Rosowsky and Edward J. Modest
8. CONTRACT OR GRANT NUMBER(s): DAMD17-74-C-4105
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Sidney Farber Cancer Center (Children's Cancer Research Foundation), 35 Binney Street, Boston, Massachusetts 02115
10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS
12. REPORT DATE: 1 August 1976
13. NUMBER OF PAGES: 57 (12) 58p.
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)
15. SECURITY CLASS. (of this report)
15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)
18. SUPPLEMENTARY NOTES
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

cordycepin
lipophilicity
membrane transport
enzymatic deamination

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The work described in this report deals with the synthesis of 3'-C-alkyl analogues of the nucleoside antibiotic cordycepin as potential antimalarial agents with enhanced liphophilicity, improved membrane transport properties and resistance to enzymatic deamination. In part the work was concerned with the synthesis of lipophilic ester and amide derivatives of Ara-A 3',5'-cyclic phosphate which might show enhanced transport into cells by passive diffusion. Thirty-three compounds were submitted to WRAIR for antimalarial assay, of which four were target cordycepin analogs of the 9-(3'-alkyl-3'-deoxyribofuranosyl)adenine type and one was a →

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

409 455

6pgs

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

BLOCK 20 (cont.)

9-(3'-alkyl-3'-deoxyxylofuranosyl)adenine.

CONTENTS

I. INTRODUCTION

This final report describes work performed during the period 1 June 1975 to 30 June 1976 on Contract No. DAMD-17-74-C-4105, U. S. Army Medical Research and Development Command, entitled "Analogs of Cordycepin and Adenine Arabinoside (Ara-A) as Potential Antimalarial Nucleosides." Reference should be made to the Annual Report, 1 June 1974 to 31 May 1975, for a summary of previous work carried out in this project. Since studies involving ara-A 3',5'-cyclic phosphate derivatives were suspended in December 1974 at the suggestion of WRAIR, the present report deals only with cordycepin analogs. Those engaged in this program have been Dr. Andre Rosowsky, Dr. Edward J. Modest, and Dr. Ayako Yamashita. A fourth investigator, Dr. Rasikkumar N. Gohil, was involved in the work until 11 August 1975. Dr. Yamashita left our group on 30 June 1976, the expiration date of the contract.

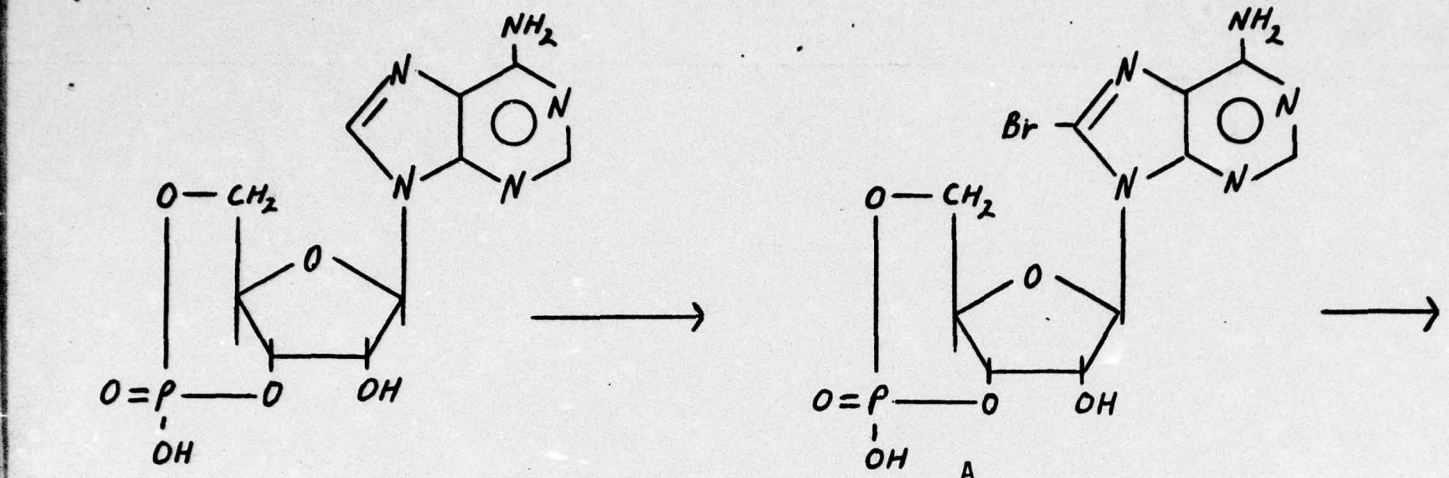
Approximately 75 compounds were prepared during the two year span of this work, of which 5 were target compounds and the rest were actual or potential intermediates. Of these, 33 compounds were submitted to WRAIR for antimalarial evaluation, including the 5 target compounds. Detailed experimental procedures and an inventory of samples submitted for bioassay are included in the Appendix (cf. Sections IIIA and IIIB). No activity was found in any of the compounds tested against P. berghei in the mouse.

II. SUMMARY OF WORK

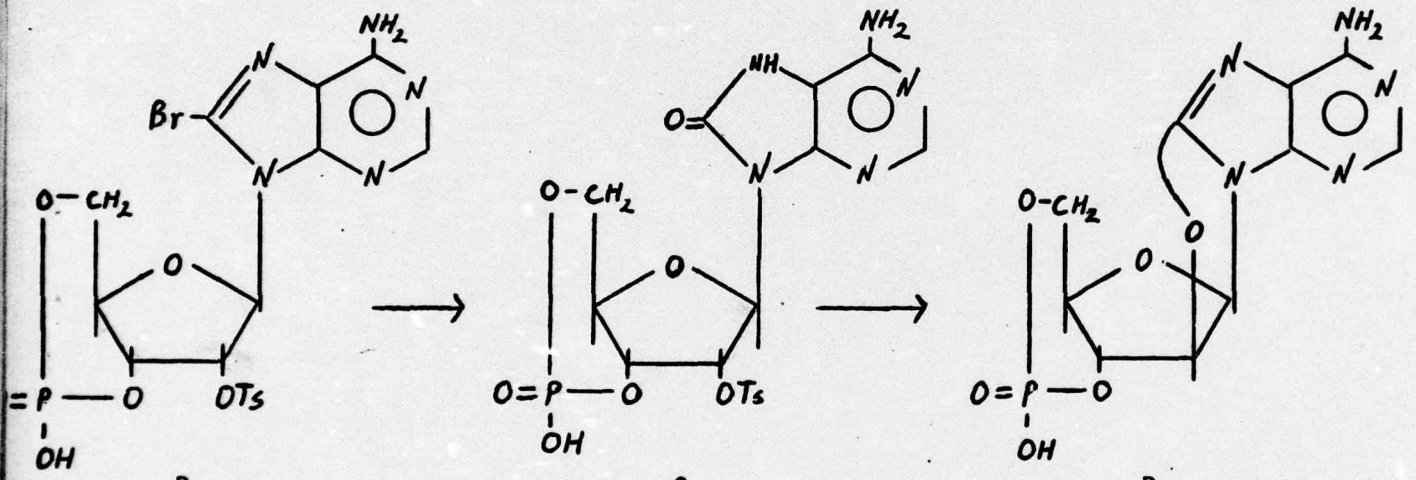
A. Synthesis

1. Adenine Arabinoside (Ara-A) Analogs

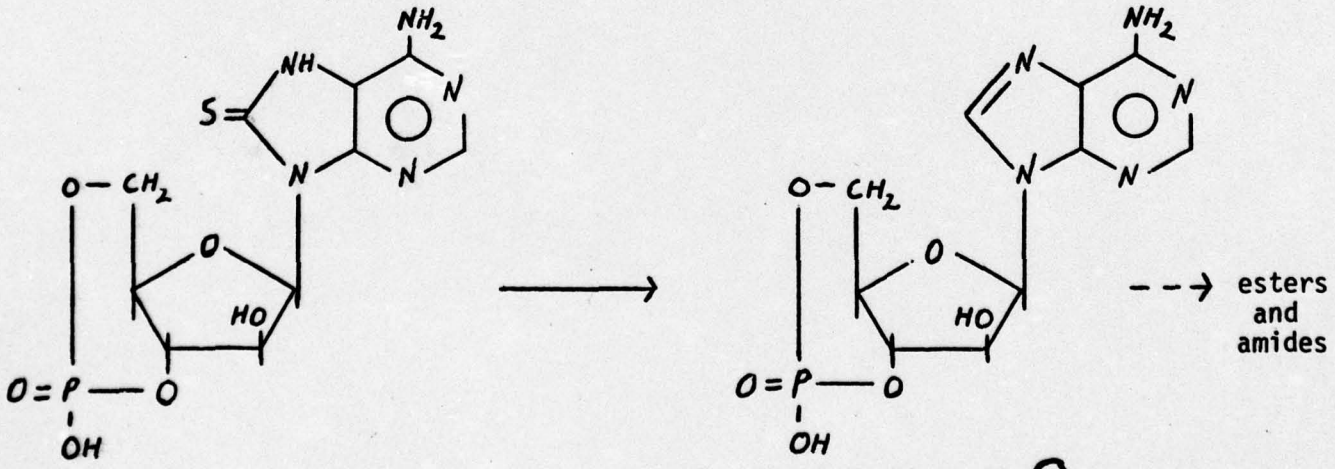
A comprehensive report of our work in this area was given in the Annual Report for the period 1 June 74 - 31 May 75. Briefly, adenosine 3',5'-cyclic phosphate (C-AMP) was brominated in NaOAc-AcOH buffer at pH 3.9 [M. Ikehara and S. Uesugi, Chem. Pharm. Bull., 17, 348 (1969)], the resultant 8-bromo derivative A was 2-O'-tosylated with p-toluenesulfonyl chloride in aqueous dioxane containing sodium hydroxide, and the tosyl ester B was heated with NaOAc-AcOH at 80° [A. Mian, R. Harris, R. W. Sidwell, R. K. Robins, and T. A. Khwaja, J. Med. Chem., 17, 259 (1974)] in order to obtain 8-hydroxy-2'-O-tosyladenosine 3',5'-cyclic phosphate (C). The latter was converted into the corresponding 8,2'-anhydronucleoside D by heating with methanolic ammonia at 80° for 6 hours, the anhydro linkage was cleaved by treatment with H_2S gas in hot DMF containing Et_3N, and the resultant 9-(β-D-arabinofuranosyl)-8-thioadenine 3',5'-cyclic phosphate E was dethiated using Davison sponge nickel. It had been our intention to carry out further esterification and amidation reactions on the cyclic phosphate moiety of the product F, but work was discontinued at this point at the suggestion of WRAIR in order to concentrate our entire effort on cordycepin analogs.



A



B C D



E F: Ara-A 3',5'-cyclic (P)

--→ esters and amides

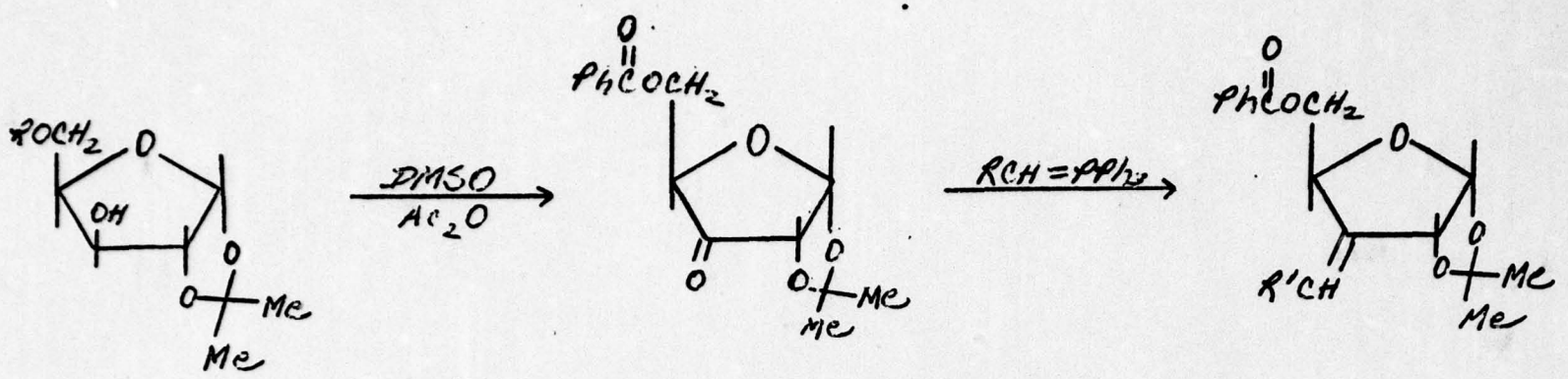
2. 9-(3'-Alkyl-3'-deoxy-β-D-ribofuranosyl)adenines

A detailed account of the synthesis of these compounds was given in our Annual Report for the period 1 June 74 - 31 May 75. In brief, 1,2-O-isopropylidene-D-xylofuranose (1) was esterified to the monobenzoate 2 and then oxidized with DMSO/Ac_2O to obtain 5-O-benzoyl-1,2-O-isopropylidene-D-erythrofuranos-3-ulose (3). On reaction with the appropriate Wittig reagents, the latter yielded olefinic derivatives 4a - 4d. Catalytic hydrogenation in the presence of 10% Pd-C occurred stereoselectively, giving the 3-alkyl-3-deoxy sugars 5a - 5d. Acetolysis led to removal of the 1,2-O-isopropylidene blocking group and afforded the diacetates 6a - 6d, and the latter were condensed with chloromercuri-6-benzamidopurine and deblocked with sodium methoxide in order to obtain the desired target compounds 7a - 7d. This series of reactions is summarized in Scheme I. Though the nucleoside coupling reactions produced a predominance of the expected β-anomer in every instance, one α-anomer was isolated in trace amount in the reaction of diacetate 6b. That this minor by-product had structure 8 was established on the basis of spectral and microanalytical data, but sufficient material was not obtained to allow testing.

3. 9-(3'-Alkyl-3'-deoxy-β-D-xylofuranosyl)adenines

During the past twelve-month period, all our effort has been devoted toward the synthesis of the 3β-alkyl compounds 9a - 9d. As will be indicated below, we succeeded in preparing enough 9a for antimalarial evaluation, but failed to obtain the higher homologues 9b - 9d.

SCHEME I

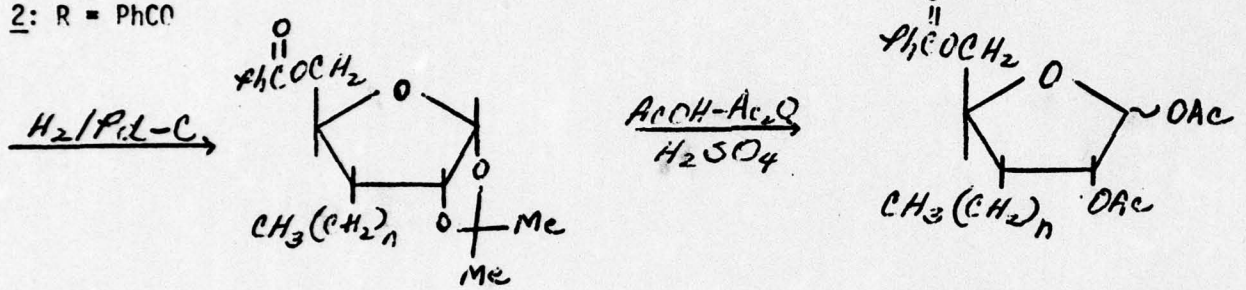


1: R = H

2: R = PhCO

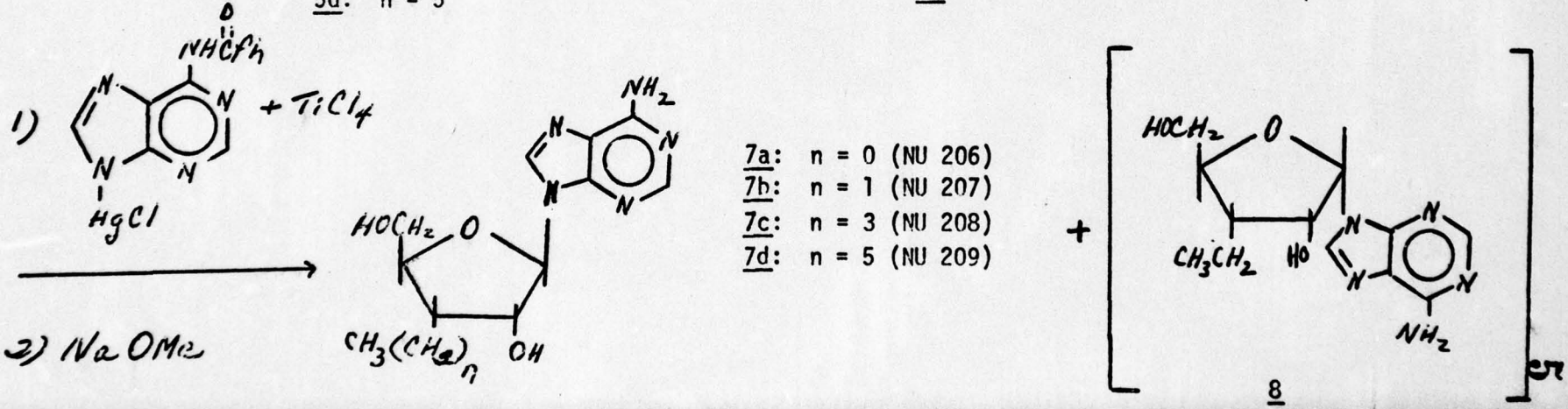
3

4a: R' = H
4b: R' = CH_2
4c: R' = $(CH_2)_2CH_2$
4d: R' = $(CH_2)_4CH_3$



5a: n = 0
5b: n = 1
5c: n = 3
5d: n = 5

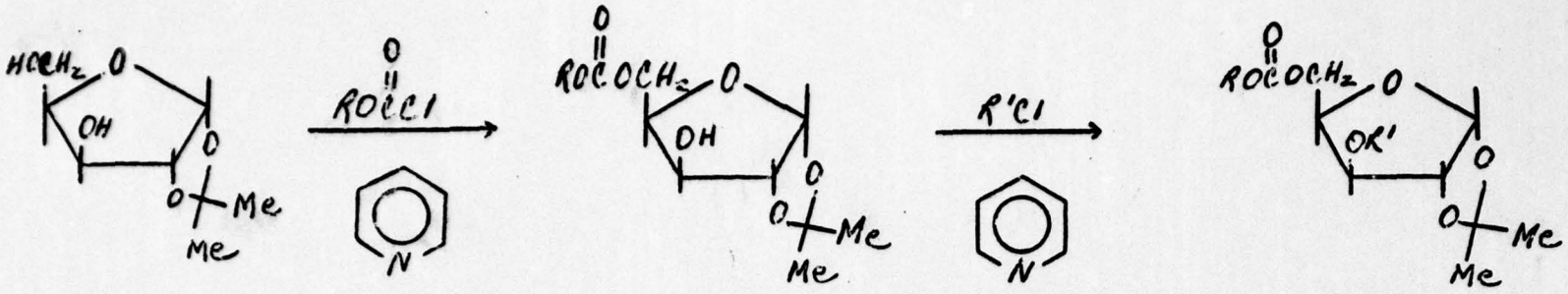
6a: n = 0
6b: n = 1
6c: n = 3
6d: n = 5



7a: n = 0 (NU 206)
7b: n = 1 (NU 207)
7c: n = 3 (NU 208)
7d: n = 5 (NU 209)

8

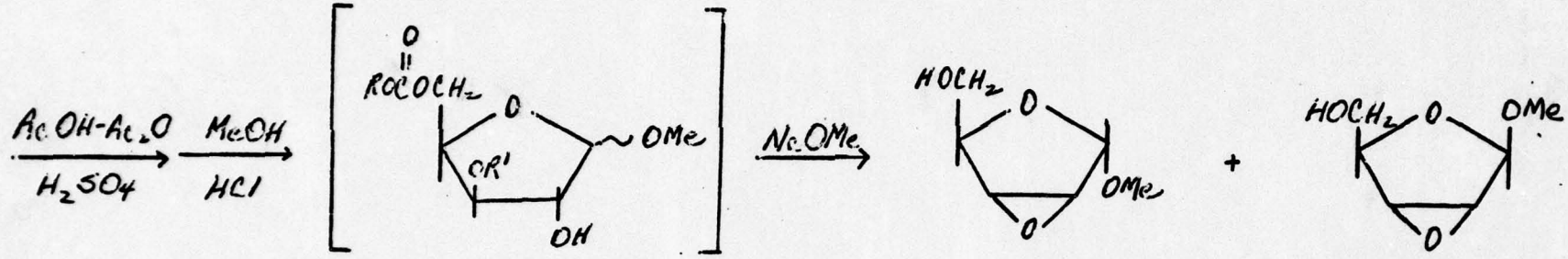
SCHEME II



1

12a: R = Me
12b: R = Et

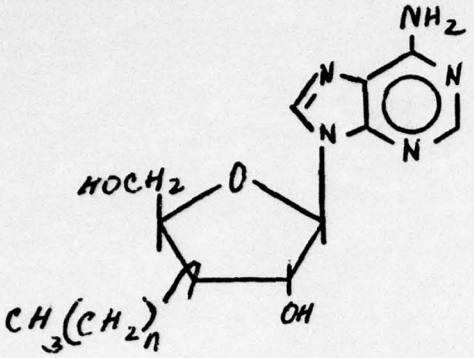
13a: R = Me, R' = Ts
13b: R = Et, R' = Ts
13c: R = Me, R = Ms
13d: R = Et, R = Ms



10

11

14a: R = Me, R'= Ts
14b: R = Et, R' = Ts
14c: R = Me, R' = Ms
14d: R = Et, R' = Ms

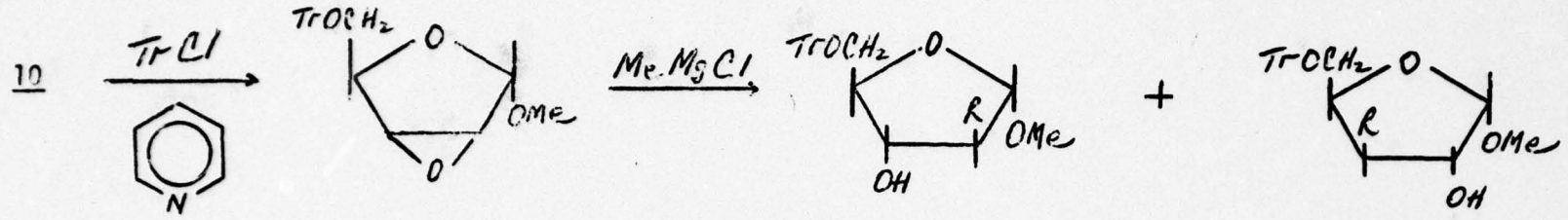


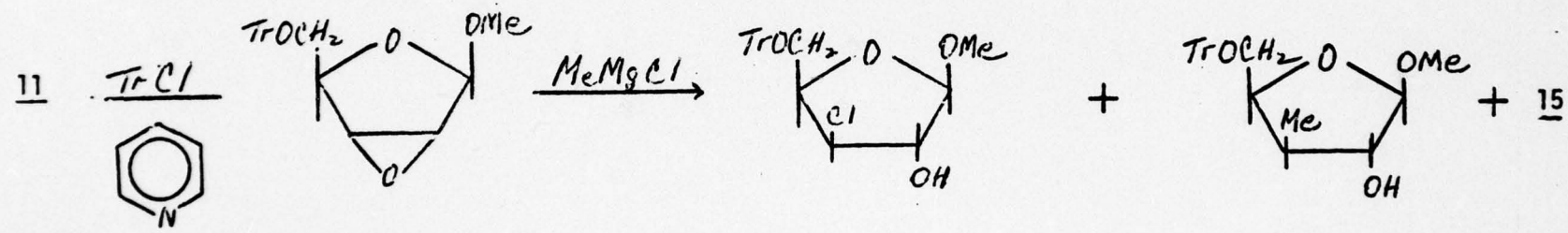
9a: n = 0
9b: n = 1
9c: n = 3
9d: n = 5

Key intermediates in the synthesis of the requisite branched sugars of this series were methyl 2,3-anhydro-α-D-ribofuranoside (10) and methyl 2,3-anhydro-β-D-ribofuranoside (11) [C. D. Anderson, L. Goodman, and B. R. Baker, J. Am. Chem. Soc., 80, 5247 (1958)]. These were obtained as shown in Scheme II. 1,2-O-Isopropylidene-D-xylofuranose was converted into the 5-O-methoxcarbonyl and 5-O-ethoxycarbonyl derivatives 12a and 12b respectively, and each of these were esterified in turn with mesyl chloride or tosyl chloride in order to obtain the four intermediates 13a - 13d. Acetolysis and acid-catalyzed methanolysis furnished the α/β-anomeric mixtures 14a - 14d, and direct treatment of these crude mixtures with sodium methoxide brought about simultaneous epoxide ring closue and cleavage of the 5-O-methoxycarbonyl or 5-O-ethoxycarbonyl blocking group. Evaluation of the four intermediates 13a - 13d did not reveal any particular advantage of one over another. However, it should be noted that the ratio of anomeric epoxides 10 and 11 was found to vary from that reported in the literature [cf. C. D. Anderson et al., op. cit.] in that the major product turned out consistently to be 11 rather than 10.

Following careful purification by vacuum distillation, the epoxides 10 and 11 were allowed to react with trityl chloride in the presence of pyridine (Scheme III)

SCHEME III


10
TrCl
N
TrOCH2
O
OMe
O
16
Me.MgCl
TrOCH2
O
R
OMe
OH
17: R = Cl
19: R = Me
+
TrOCH2
O
R
OMe
OH
18: R = Cl
20: R = Me


11
TrCl
N
TrOCH2
O
OMe
O
15
MeMgCl
TrOCH2
O
OMe
Cl
OH
21
+
TrOCH2
O
OMe
Me
OH
22
+ 15

and the resultant 5-O-trityl derivatives 15 and 16 were treated with methylmagnesium chloride as described in the literature [S. R. Jenkins and E. Walton, Carbohyd. Res., 26, 71 (1973)]. The reaction of the α-anomer 16 with MeMgCl in ether (2 days at room temperature produced a 60 - 70% yield of a mixture of methyl 2-chloro-2-deoxy-5-O-trityl-α-D-arabinofuranoside (17) and methyl 3-chloro-3-deoxy-5-O-trityl-α-D-xylofuranoside (18), a 10% yield of methyl 2-deoxy-2-methyl-5-O-trityl-α-D-arabinofuranoside (19), and a 15% yield of methyl 3-deoxy-3-methyl-5-O-trityl-α-D-xylofuranoside (20). The four products could be identified readily on tlc plates on the basis of their color after spraying with 1,3-naphthalenediol-H_3PO_4-EtOH reagent and heating (cf. S. R. Jenkins and E. Walton, op. cit.), and their structures were confirmed on the basis of nmr spectra and, with compounds 19 and 20, by elemental analysis. The formation of both possible chloro compounds 17 and 18, and also the very high combined yield of these compounds relative to the methyl adducts 10 and 20, were at variance with the published report (S. R. Jenkins and E. Walton, op. cit.) that 20 can be isolated in 48% yield. The reason for this discrepancy is unknown, and attempts to increase the proportion of alkylated products by adding hexamethylphosphoramide to the Grignard reaction solvent were not successful.

The reaction of the β-anomeric trityl derivative 15 with MeMgCl in ether or THF containing a small amount of benzene likewise failed to proceed in the expected manner (cf. S. R. Jenkins and E. Walton, op. cit.). At least 90% of the starting material was recovered unchanged even after refluxing for a week in the presence of a large excess of Grignard reagent. There was approximately 3 - 5% each of methyl 3-chloro-3-deoxy-5-O-trityl-β-D-xylofuranoside (21) and methyl 3-deoxy-3-methyl-5-O-trityl-β-D-xylofuranoside (22), but no evidence of any of the corresponding 2-chloro-2-deoxy or 2-methyl-2-deoxy adducts. The published claim that a 50% yield of compound 22 is obtainable from epoxide 15 could not be substantiated despite repeated attempts.

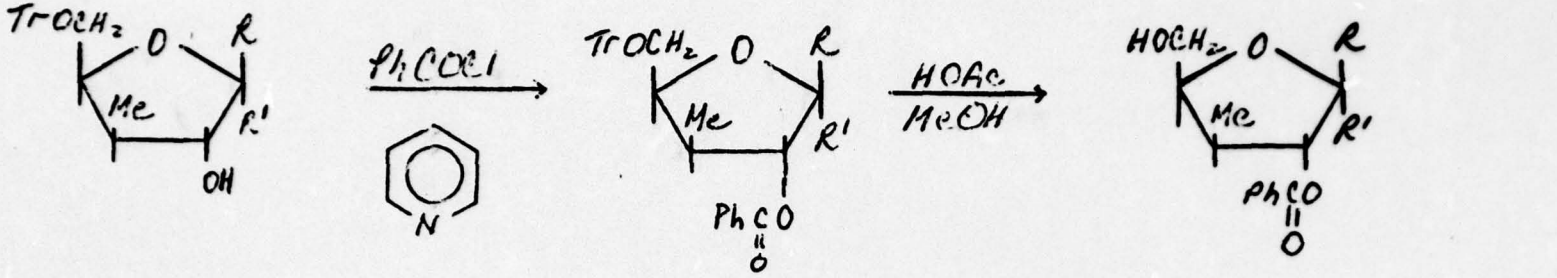
After sufficient quantities of the 3-deoxy-3-methyl compounds 20 and 22 had

been accumulated, it became possible to achieve the synthesis of the target nucleoside 9a as shown in Scheme IV. It should be stressed that the disappointingly low yield of compounds 20 and 22 via the Grignard route created a serious problem of supply. We explored several alternative routes to these key intermediates. One such route involved the use of dimethyl lithium cuprate, and another of 1,3-dithianyl-2-lithium (the latter reagent will be discussed below; see p. 13 of this report).

3-O-Benzoylation of 20 gave 23, which was detritylated readily to 25, 5-O-benzoylated to 27, acetolyzed to 29, and converted to chloro sugar 30 by treatment with dry HCl in ether. Similarly, the β-anomer 22 was transformed successively into 24, 26, 28, 29, and 30. The overall yield for these five steps was satisfactory, and there was no particular advantage to the 20 → 30 route over the 22 → 30 route. All the compounds except 20 and 22 were oils or syrups, but were nonetheless quite easy to purify by column chromatography on silica gel and to characterize by ir and nmr spectral means. Condensation of 30 with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride and Celite ([J. Prokop and D. H. Murray, J. Pharm. Sci., 54, 359 (1965); D. H. Murray and J. Prokop, ibid, 54, 1468 (1965)] furnished the target nucleoside 9a in about 60% yield after deprotection with sodium methoxide in refluxing methanol. The properties of our product were in substantial agreement with those reported earlier (cf. S. R. Jenkins and E. Walton, op. cit.). A trace of the α-anomer was detected by tlc but the compound was not isolated.

Because epoxide 11 was available in greater quantity than epoxide 10 via the route shown in Scheme II, our entire supply of 10 was consumed in the preparation of 9a. Preliminary work on the synthesis of the higher homologues 9b - 9d was performed with the more abundant, but unfortunately less reactive, epoxide 11. At the time of expiration of the contract, this work remains incomplete, but can nonetheless be summarized briefly.

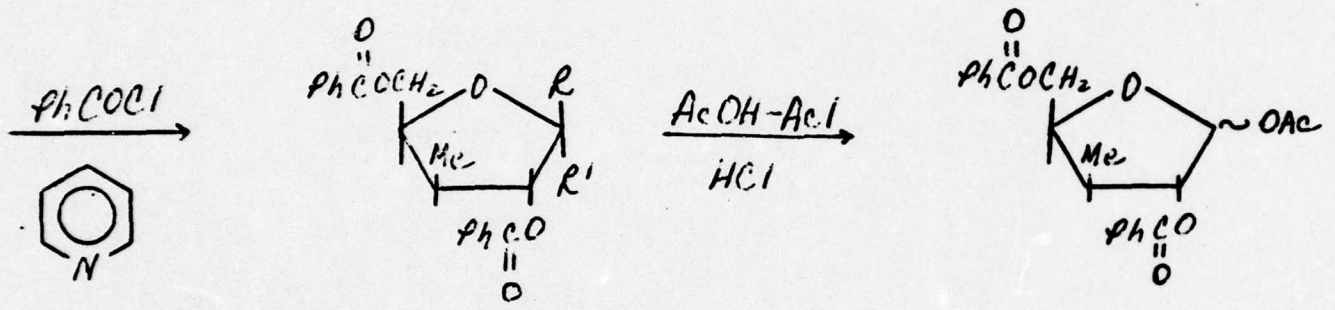
SCHEME IV



20: R = H, R' = MeO
22: R = MeO, R' = H

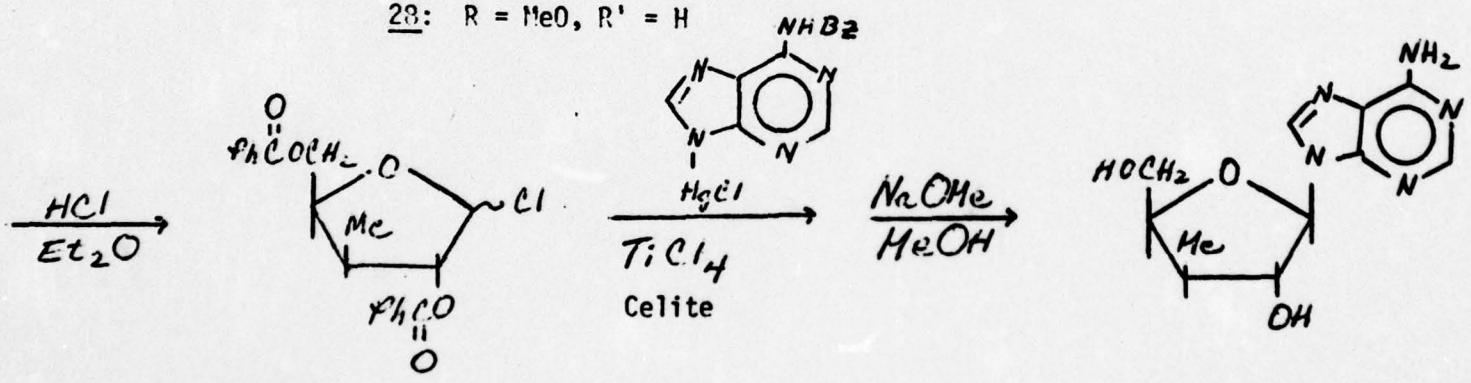
23: R = H, R' = MeO
24: R = MeO, R' = H

25: R = H, R' = MeO
26: R = MeO, R' = H



27: R = H, R' = Me
28: R = MeO, R' = H

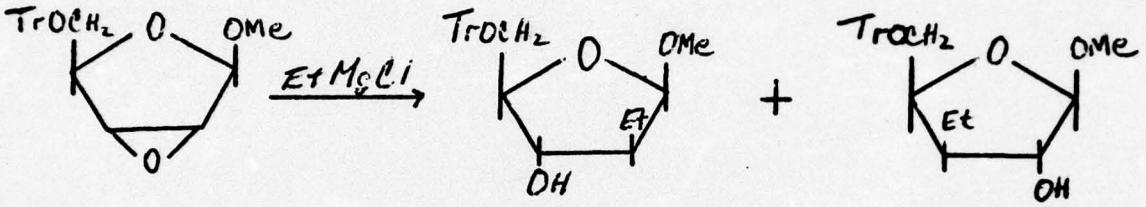
29



30

9a (NU 211)

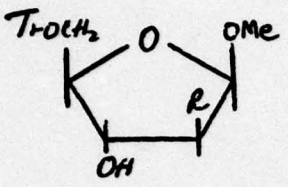
Reaction of epoxide 11 with ethylmagnesium chloride took an unexpected course, in that attack appeared to proceed both at C_2 to give methyl 2-deoxy-2-ethyl-5-O-trityl-β-D-arabinofuranoside (31, 16% yield) and methyl 3-deoxy-3-ethyl-5-O-trityl-β-D-xylofuranoside (32, 8% yield). Some chloro compounds were also formed but were not isolated and characterized.

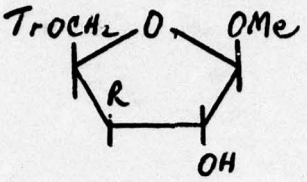


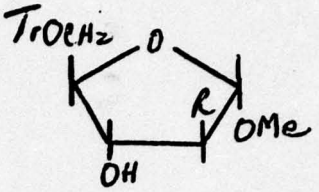
11 31 32

Although epoxide 11 unaccountably failed to react with n-butylmagnesium chloride, it did react with n-hexylmagnesium bromide to give a complex mixture of products from which four discrete products were recovered by column chromatographic and preparative tlc purification. Three of these were formulated as methyl 2-bromo-2-deoxy-5-O-trityl-β-D-xylofuranoside (33, 5% yield), methyl 3-bromo-3-deoxy-5-O-trityl-β-D-xylofuranoside (34, 46% yield), and methyl 2-deoxy-2-n-hexyl-5-O-trityl-β-D-arabinofuranoside (35, 9% yield). A 16% yield of unchanged 11 was also recovered. The fourth product (only 2% yield) was initially thought to be the desired methyl 3-deoxy-3-n-hexyl-5-O-trityl-β-D-xylofuranoside (36), but it now appears the correct structure for this minor component is methyl 2-deoxy-2-n-hexyl-5-O-trityl-α-D-arabinofuranoside (37). The strongest evidence in favor of this conclusion is that, when the usual sequence of 3-O-benzoylation, detritylation, 5-O-benzoylation, and acetolysis was carried out, extensive decomposition occurred. Attempted nucleoside fusion via the titanium tetrachloride-Celite procedure led to the isolation of adenine as the sole identifiable product. This behavior duplicated that observed in separate experiments using methyl 2-deoxy-

2-methyl-5-O-trityl-α-D-arabinofuranoside, another 2β-alkyl-2-deoxy sugar (see below).







33: R = Br
35: R = n-C_6H_{13}

34: R = Br
36: R = n-C_6H_{13}

37: R = n-C_6H_{13}

The unusually complex product mixture obtained in the n-hexylmagnesium bromide reaction suggests that the starting epoxide 11 may have been contaminated with a very small amount (< 5%) of the α-anomeric epoxide 10. This would explain the formation of compound 37 and might account for the several other unidentified trace products observed in the mixture. Whether or not the desired 3-deoxy-3-n-hexyl compound 36 was actually present in the mixture was still unknown at the time the work was discontinued.

Since the Grignard reaction appeared to be a very troublesome method of synthesis of 3-alkyl-3-deoxy sugars, we sought an alternative approach in the reaction of epoxide 10 with 1,3-dithian-2-yl lithium. This reagent has been used successfully with other sugar epoxides [A. M. Sepulchre, G. Lukacs, G. Vass, and S. D. Gero, Bull. Soc. Chim. Fr., 4000 (1972)]. We hoped that its main advantage over Grignard reagents would be the absence of halohydrin byproducts. But, although we had expected 1,3-dithian-3-yl lithium to react with epoxide 10 at both C_3 and C_2, it turned out that attack by this particular reagent was quite regiospecific at C_2. Thus, we had inadvertently discovered a new route to 2-alkyl-2-deoxy-D-arabinose derivatives, and we chose to explore the possibility of synthesizing the heretofore unknown nucleoside 9-(2'-deoxy-2'-methyl-β-D-arabinofuranosyl)-adenine via this approach. The chemical sequence we followed is summarized in

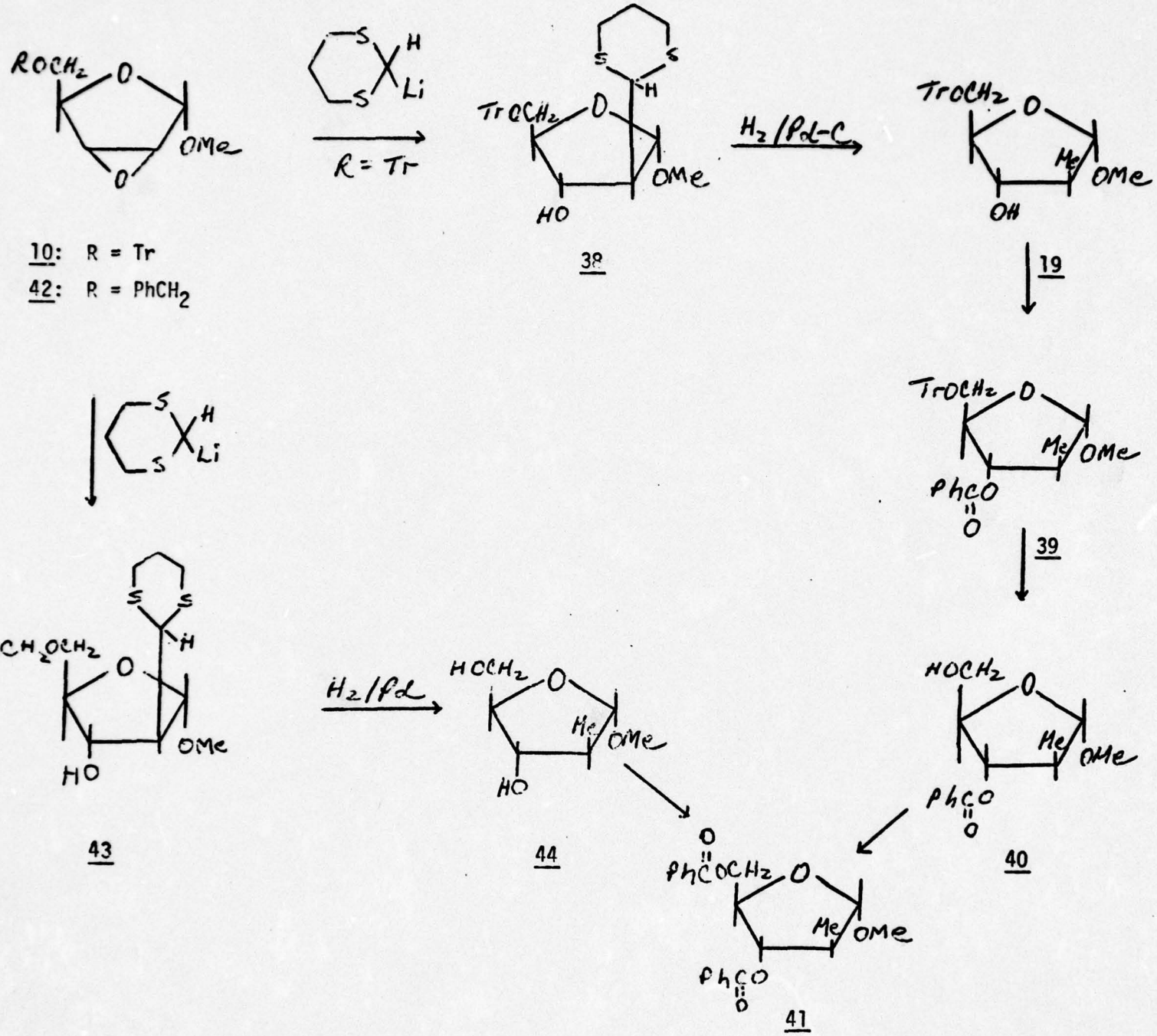
Scheme V.

Epoxide 10 was allowed to react with 1,3-dithian-2-yl lithium which was generated immediately before use by treatment of 1,3-dithiane with n-butyl lithium. A single product was formed in excellent yield, whose elemental analysis was in agreement with a dithiane adduct and whose nmr spectral data were consistent with attack at C_2 of the anhydro sugar to produce structure 38. Catalytic dethiation of 38 readily gave a methyl-substituted sugar whose identity was established as 19 by comparison with the sample prepared via the Grignard route. 3-O-Benzoylation, detritylation, and 5-O-benzoylation converted this material into compounds 39, 40, and 41 respectively. All these sugars were oils, but could be purified easily by column chromatography, and were characterized thoroughly by microchemical analysis and on the basis of nmr spectra. Unfortunately attempts to convert 41 into a nucleoside via the usual chloromercuri-6-benzamidopurine/titanium tetrachloride/chloro sugar sequence gave only black tar and adenine. Hence it appears that 2-alkyl-2-deoxyfuranose sugars are very acid-labile and require special conditions in the nucleosidation reaction.

Because we felt the regioselectivity displayed in the reaction of 10 with 1,3-dithian-2-yl lithium might be due to steric hindrance at C_3 by the 5-O-trityl substituent, we also investigated this reaction using methyl 2,3-anhydro-5-O-benzyl-α-D-ribofuranoside (42) which we synthesized by the sequence shown in Scheme VI and discussed below. The nature of the protecting group appeared not to alter the regioselectivity of the reaction since 42 yielded only a single product whose spectral and microanalytical properties were in accord with structure 43. Catalytic dethiation of 43 led conveniently to methyl 2-deoxy-2-methyl-α-D-arabinofuranoside (44) by simultaneous reductive debenzylation, and 3,5-di-O-benzoylation of 44 gave 41 which was identical with the material derived from 40.

The preparation of epoxide 42 was accomplished conveniently by a new route starting from 1,2-O-isopropylidene-D-xylofuranose (1). 5-O-Tosylation to 45 and

SCHEME V



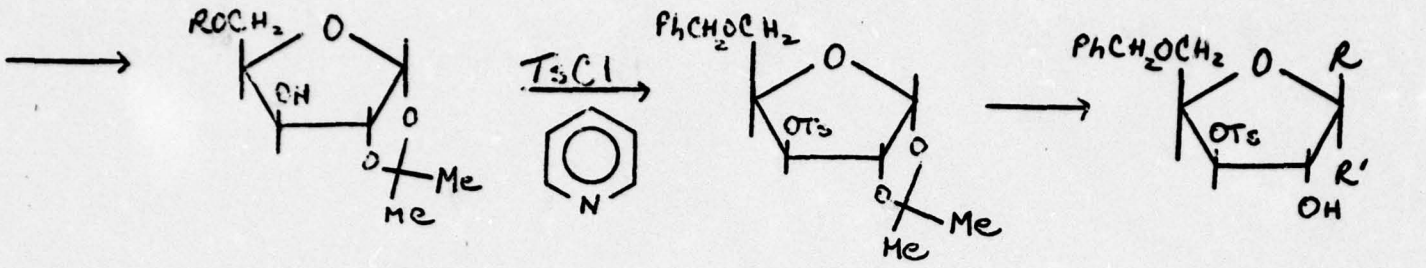
10: R = Tr

42: R = $PhCH_2$

displacement with sodium benzylate to 46 was carried out as described in the literature [H. Kuzuhara and S. Emoto, Agr. Biol. Chem., 28, 900 (1964)]. Further tosylation of 46 yielded the 3-O-tosyl derivative 47, which was methanolyzed in the presence of acid to a mixture of α- and β-anomers 48a and 48b. Without separation, the mixture was treated wtih sodium methoxide in order to effect closure of the epoxide ring. The resulting epoxides 49a and 49b could be separated by column chromatography and were characterized adequately by spectral and microanalytical means, as well as by reference to the literature [J. A. Wright and N. F. Taylor, Carbohyd. Res., 6, 347 (1968); J. A. Wright, N. F. Taylor, and J. J. Fox, J. Org. Chem., 34, 2632 (1969)].

As indicated in Scheme VI, the 5-O-benzyl-1,2-O-isopropylidene derivative 46 was also investigated briefly as a possible precursor to 3β-alkyl-3-deoxy sugars of the kind needed for the synthesis of nucleosides 7a - 7d. Oxidation of the 3-hydroxyl group in 46 with DMSO and acetic anhydride gave 5-O-benzyl-1,2-O-isopropylidene-D-erythros-3-ulofuranose (50), and Wittig condensation of the latter with triphenylphosphinemethylene furnished the olefinic sugar 51. Catalytic hydrogenation of 51 yielded 5-O-benzyl-3-deoxy-1,2-O-isopropylidene-3-methyl-D-ribofuranose (52). Although this compound could have served as a precursor to 7a (cf. Scheme I) we chose not to pursue this approach because removal of a 5-O-benzoyl group seemed easier than removal of a 5-O-benzyl group, and because 5-O-benzoyl derivatives were more easily detected on tlc by virtue of their stronger absorbance under ultraviolet light.

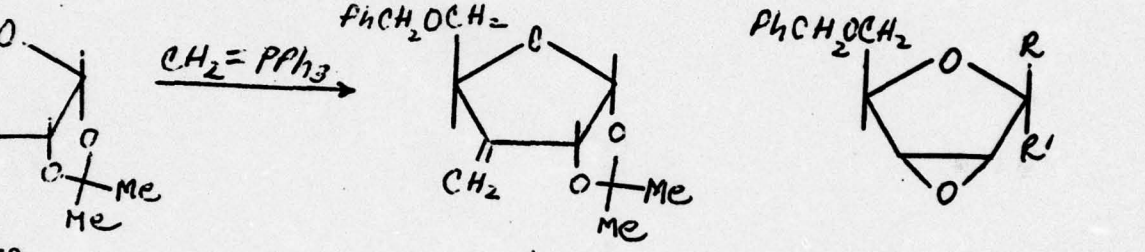
SCHEME VI



45: R = TsO
46: R = $PhCH_2$

47

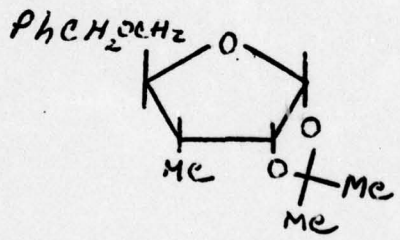
48a: R = MeO
R' = H
48b: R = H,
R' = MeO



50

51

49a: R = MeO
R' = H
49b: R = H
R' = MeO



52

B/ Biological Evaluation

As of 30 June 76 we had submitted to WRAIR for antimalarial assay a total of 39 samples representing 5 target nucleosides and 24 intermediates. The names, code numbers, bottle numbers, and other data for these samples are given in Appendix IIIB.

Assay data have been received for 22 compounds against Plasmodium berghei in the mouse. None of them showed significant activity up to the highest dose tested (640 mg/kg).

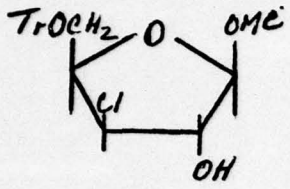
III. APPENDIX

A. Compounds Synthesized (1 June 75 to 30 June 76)

Names, structures and experimental procedures for intermediates and target compounds synthesized during the period covered by this report are given in the following pages (20 - 54). Data and procedures for intermediates and target compounds synthesized during the first twelve-month period of this contract have been submitted previously (cf. Annual Report, 1 June 74 - 31 May 75, pp. 22 - 52).

EXPERIMENTAL REPORT FORM

Compound(s):

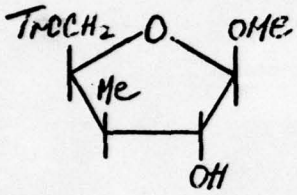


Name: Methyl 3-chloro-3-deoxy-5-O-trityl-β-D-xylofuranoside

Code Number: AM 312

Empirical formula: $C_{25}H_{25}ClO_4$

Molecular weight: 424.93



Name: Methyl 3-deoxy-3-methyl-5-O-trityl-β-D-xylofuranoside

Code Number: AM 337

Empirical formula: $C_{26}H_{28}O_4$

Molecular weight: 404.51

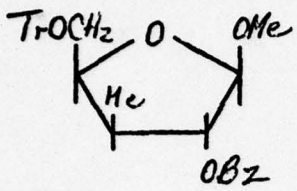
Procedure:

A stirred solution of methyl 2,3-anhydro-5-O-trityl-β-D-ribofuranoside (29 g, 0.074 mol) in a mixture of benzene (90 ml) and ether (900 ml) was treated dropwise with 1 M methylmagnesium chloride solution in ether (58 ml, 0.182 mol). After 15 hr of refluxing, a second portion of Grignard solution (29 ml, 0.091 mol) was added, and heating was resumed for another 20 hr. A third portion of Grignard solution (29 ml, 0.091 mol) was added and refluxing was continued for a total of 140 hr. The reaction mixture was poured into a solution of ammonium chloride (290 g) in water (1600 ml), ether (360 ml) was added, and the layers were separated. The aqueous layer was extracted with ether (4 x 725 ml), and the combined ether solutions were washed successively with 10% ammonium chloride (725 ml), saturated sodium bicarbonate (540 ml), and water (2 x 540 ml). Evaporation gave a solid (26 g) whose tlc (silica gel, 4:1 C_6H_6-EtOAc) showed spots at R_f 0.8, 0.45, and 0.3.

The spots were visualized by spraying the dried tlc plate with 1,3-naphthalenediol-H_3PO_4-EtOH reagent [S. R. Jenkins and E. Walton, Carbohyd. Res., 26, 71 (1973)] and heating on a steam cone. The spots gave the following colors: 0.8 (blue-green), 0.45 (maroon), 0.3 (pinkish tan). It was evident on inspection of spot intensities that the fastest moving spot, corresponding to unreacted epoxide, represents ca. 90% of the mixture and that the other 2 components only account for about 5% each. The chloro and alkyl compounds were separated by column chromatography on silica gel, with 19:1 C_6H_6-EtOAc as the eluent. Methyl 3-deoxy-3-methyl-5-O-trityl-β-D-xylofuranoside showed the following nmr signals: τ ($CDCl_3$) 9.15 (d, J = 7.5 Hz, C_3-Me), 7.6 - 8.2 (m, C_3-H), 6.9 (d, J = 5 Hz, C_5-H), 6.5 (S, MeO), 5.9 - 6.1 and 5.4 - 5.7 (m, C_2-H and C_4-H), 5.23 (d, J $\leq$ 2 Hz), 2.4 - 2.9 (m, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2-O-benzoyl-3-deoxy-3-methyl-5-O-trityl-β-D-xylofuranoside

Code number: AM 344

Empirical formula: $C_{32}H_{32}O_5$

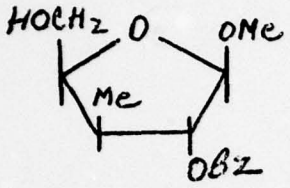
Molecular weight: 496.6

Procedure:

A solution of methyl 3-deoxy-3-methyl-5-O-trityl-β-D-xylofuranoside (3.0 g, 0.0074 mol) in dry pyridine (60 ml) was treated with benzoyl chloride (1.9 ml, 0.015 mol). The mixture was stirred at room temperature overnight and then poured into ice water. The product was extracted with chloroform (3x), and the combined organic layers were washed successively with cold 4% hydrochloric acid, saturated sodium bicarbonate, and water. Solvent evaporation, followed by removal of the last traces of pyridine by azeotropic distillation with toluene, gave a colorless solid (3.5 g, 96%); R_f 0.56 (silica gel, 40:1 C_6H_6-EtOAc); nmr: τ ($CDCl_3$) 9.0 (d, J = 7.5 Hz, C_3-Me), 7.3 - 7.6 (m, C_3-H), 6.4 - 7.0 (complex m, C_5-H), 6.6 (s, MeO), 5.3 - 5.6 (m, C_4-H), 4.96 (s, C_2-H), 4.90 (d, J $\leq$ 2Hz, C_1-H), 1.8 - 2.9 (complex m, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2-O-benzoyl-3-deoxy-3-methyl-β-D-xylofuranoside

Code number: AM 345

Empirical formula: $C_{14}H_{18}O_5$

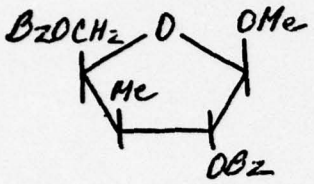
Molecular weight: 266.32

Prodedure:

A solution of methyl 2-O-benzoyl-3-deoxy-3-methyl-5-O-trityl-β-D-xylofuranoside (3.5 g, 0.007 mol) in acetic acid (25 ml), water (18 ml), and methanol (140 ml) was refluxed for 16 hr, cooled, and evaporated to dryness under reduced pressure. After removal of all the acetic acid by repeated azeotropic distillation with methanol, the residue was chromatographed (silica gel, 19 : 1 C_6H_6-EtOAc) to give a pale yellow oil (1.4 g, 75% yield); R_f 0.32 (silica gel, 19:1 C_6H_6-EtOAc); nmr: τ ($CDCl_3$) 8.7 (d, J = 7.5 Hz, C_3-Me), 7.0 - 7.6 (m, C_3-H), 6.5 (s, MeO), 6.2 (broad d, J = 4 Hz, C_5-H), 5.3 - 5.8 (m, C_4-H), 4.9 (d, J = 2.0 Hz, C_1-H), 4.75 (dd, C_2-H), 1.8 - 2.6 (complex m, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2,5-di-O-benzoyl-3-deoxy-3-methyl-β-D-xylofuranoside

Code number: AM 346

Empirical formula: $C_{21}H_{22}O_6$

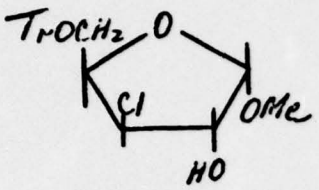
Molecular weight: 370.43

Procedure:

A solution of methyl 2-O-benzoyl-3-deoxy-3-methyl-β-D-xylofuranoside (1.4 g, 0.0053 mol) in dry pyridine (45 ml) was treated with benzoyl chloride (1.5 ml, 0.011 mol). The mixture was stirred at room temperature overnight and then poured into ice water. Extraction with chloroform and chromatography in silica gel (39:1 C_6H_6-EtOAc) gave a pale yellow oil (1.9 g, 100% yield); R_f 0.52 (silica gel, 20:1 C_6H_6-EtOAc); nmr: τ ($CDCl_3$) 8.7 (d, J = 7.5 Hz, 3-Me), 7.2 - 7.5 (m, C_3-H), 6.6 (s, OMe), 5.1 - 5.9 (complex m, C_4-H and C_5-H), 4.9 (s, C_2-H), 4.82 (s, J = 2.0 Hz, C_1-H), 1.7 - 2.7 (complex m, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound(s):

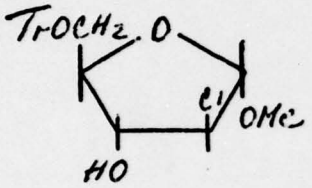


Name: Methyl 3-chloro-3-deoxy-5-O-trityl-α-D-xylofuranoside

Code number: AM 316

Empirical formula: $C_{25}H_{25}ClO_4$

Molecular weight: 424.93

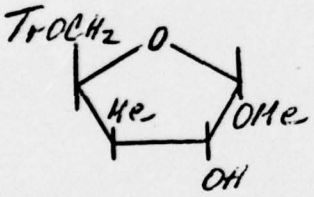


Name: Methyl 2-chloro-2-deoxy-5-O-trityl-α-D-arabinofuranoside

Code number: AM 313

Empirical formula: $C_{25}H_{25}ClO_4$

Molecular weight: 424.93

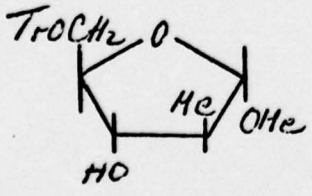


Name: Methyl 3-deoxy-3-methyl-5-O-trityl-α-D-xylofuranoside

Code number: AM 340

Empirical formula: $C_{26}H_{28}O_4$

Molecular weight: 404.51



Name: Methyl 2-deoxy-2-methyl-5-O-trityl-α-D-arabinofuranoside

Code number: AM 320

Empirical formula: $C_{26}H_{28}O_4$

Molecular weight: 404.51

Procedure:

A. A stirred solution of methyl 2,3-anhydro-5-O-trityl-α-D-ribofuranoside (2.0 g, 0.0052 mol) in ether (100 ml) was cooled to 0^0 and treated dropwise with 3.2 M methylmagnesium chloride in tetrahydrofuran (10 ml, 0.032 mol). After 2 days at room temperature the mixture was poured into a mixture of aqueous ammonium chloride, ice, and ether. The aqueous layer was separated and washed with ether, and the extracts were combined and evaporated. Fractionation of the crude product by column chromatography (silica gel, 20:1 C_6H_6-EtOAc) yielded the following products: 1) methyl 2-chloro-2-deoxy-5-O-trityl-α-D-arabinofuranoside and methyl 3-chloro-3-deoxy-5-O-trityl-α-D-xylofuranoside (mixture of isomers), 1.5 g (67% yield); 2) methyl 3-deoxy-3-methyl-5-O-trityl-α-D-xylofuranoside, 0.31 g (15% yield); 3) methyl 2-deoxy-2-methyl-5-O-trityl-α-D-arabinofuranoside, 0.20 g (10% yield). The mixture of chloro compounds gave a blue-green color on spraying of the tlc plate with 1,3-naphthalenediol-H_3PO_4-EtOH reagent, and showed the following nmr signals: τ ($CDCl_3$) 7.2 - 7.5 and 5.4 - 6.0 (m, C_2-H, C_3-H, and C_4-H), 6.4 - 6.9 (m, C_5-H), 6.4 and 6.3 (S, MeO),5.03 (d, $J \leq 2$ Hz, C_1-H of the 2-chloro-2-deoxy isomer), 4.75 (d, J = 4.0 Hz, C_1-H of the 3-chloro-3-deoxy isomer), 2.4 - 2.9 (m, aromatic protons). The 3-deoxy-3-methyl compound gave a yellow-pink spot and showed the following signals: τ ($CDCl_3$) 9.1 (d, J = 7 Hz, C_3-Me), 7.5 - 8.0 (m, C_3-H), 6.6 - 7.2 (m, C_5-H), 6.5 (s, MeO), 5.6 - 6.2 (m, C_2-H and C_4-H), 5.05 (d, J = 4 Hz, C_1-H), 2.5 - 3.0 (m, aromatic protons). The 2-deoxy-2-methyl compound (maroon spot) gave the following nmr signals: τ ($CDCl_3$) 9.0 (d, J = 7.5 Hz, C_2-Me), 7.3 - 8.2 (m, C_2-H), 6.2 - 7.2 (m, C_3-H and C_5-H), 6.6 (s, MeOH), 5.7 - 6.1 (m, C_4-H), 5.37 (d, $J \leq 2$ Hz, C_1-H), 2.4 - 3.0 (m, aromatic protons).

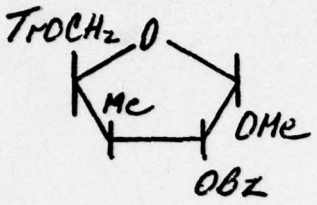
B. A stirred solution of methyl 2,3-anhydro-5-O-trityl-α-D-ribofuranoside (5.0 g, 0.013 mol) in ether (250 ml) was cooled to 0^0 and treated dropwise with 3.2 M methylmagnesium chloride in tetrahydrofuran (30 ml, 0.096 mol) under a nitrogen atmosphere. A white precipitate formed immediately. The reaction mixture was stirred at room temperature for 3 days and then under reflux for 5 hr, and was

worked up as in the preceding experiment. Analysis of the crude product by tlc (silica gel, 10:1 C_6H_6-EtOAc, 1,3-dihydroxynaphthalene-H_3PO_4-EtOH spray reagent) showed the following spots: R_f 0.58 and 0.61 (blue green, 3-chloro-3-deoxy and 2-chloro-2-deoxy compounds); R_f 0.43 (yellow-pink, 3-deoxy-3-methyl compound); R_f 0.33 (maroon, 2-deoxy-2-methyl compound). Column chromatography (silica gel, 1:99 to 5:95 C_6H_6-EtOAc) afforded the following fractions: 1) methyl 2-chloro-2-deoxy-5-O-trityl-α-D-arabinofuranoside and methyl 3-chloro-3-deoxy-5-O-trityl-α-D-arabinofuranoside and methyl 3-chloro-3-deoxy-5-O-trityl-α-D-xylofuranoside (mixture of isomers), 3.9 g (71% yield); 2) methyl 3-deoxy-3-methyl-5-O-trityl-α-D-xylofuranoside, 1.0 g (16% yield); 3) methyl 2-deoxy-2-methyl-5-O-trityl-α-D-arabinofuranoside, 0.6 g (9.6% yield). The 3-deoxy-3-methyl isomer was sent for microanalysis.

Calcd. for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.09; H, 6.92.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2-O-benzoyl-3-deoxy-3-methyl-5-O-trityl-α-D-xylofuranoside

Code number: AM 341

Empirical formula: $C_{32}H_{32}O_5$

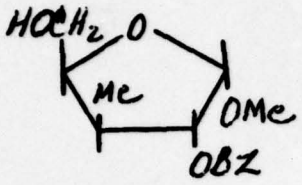
Molecular weight: 496.6

Procedure:

A solution of methyl 3-deoxy-3-methyl-5-O-trityl-α-D-xylofuranoside (1.8 g, 0.0045 mol) in dry pyridine (36 ml) was treated with benzoyl chloride (1.1 ml). The mixture was stirred at room temperature overnight and then poured into ice water. The product was extracted into chloroform (3x), and the combined organic layers were washed successively with cold 4% hydrochloric acid, saturated sodium bicarbonate, and water. Drying and evaporation gave a syrup from which the last traces of pyridine were removed by azeotropic distillation with toluene. The product was a yellow gum (1.9 g, 84% yield); R_f 0.40 (silica gel, 40:1 C_6H_6-EtOAc); nmr: τ ($CDCl_3$) 9.0 (d, J = 7.5 Hz, C_3-Me), 6.5 - 7.2 (complex m, C_3-H and C_5-H), 6.5 (s, MeO), 5.4 - 5.8 (m, C_4-H), 4.9 (dd, C_2-H), 4.58 (d, J = 4 Hz, C_1-H), 1.8 - 2.8 (complex m, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2-O-benzoyl-3-deoxy-3-methyl-α-D-xylofuranoside

Code number: AM 342

Empirical formula: $C_{14}H_{18}O_5$

Molecular weight: 266.32

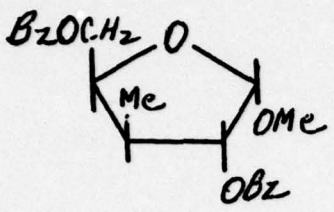
Procedure:

A solution of methyl 2-O-benzoyl-3-deoxy-3-methyl-5-O-trityl-α-D-xylofuranoside (1.8 g, 0.0036 mol) in acetic acid (12 ml), water (9 ml) and methanol (70 ml) was refluxed for 16 hr, cooled, and evaporated to dryness under reduced pressure. After removal of all the acetic acid by repeated azeotropic distillation with methanol, the residue was chromatographed (silica gel, 10:1 C_6H_6-EtOAc) to give a colorless oil (0.75 g, 78% yield); R_f 0.23 (silica gel, 4:1 C_6H_6-EtOAc); nmr: τ ($CDCl_3$) 8.85 (d, J = 7 Hz, C_3-Me), 7.0 - 7.6 (m, C_3-H), 6.5 (s, MeO), 6.2 - 6.4 (broad d, J = 4 Hz, C_5-H), 5.6 - 6.0 (m, C_4-H), 5.2 (dd, C_2-H), 4.77 (d, J = 4 Hz, C_1-H), 1.8 - 2.8 (complex m, aromatic protons).

Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.27; H, 6.88.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2,5-di-O-benzoyl-3-deoxy-3-methyl-α-D-xylofuranoside

Code number: AM 343

Empirical formula: $C_{21}H_{22}O_6$

Molecular weight: 370.43

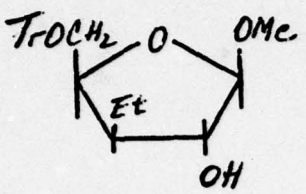
Procedure:

A solution of methyl 2-O-benzoyl-3-deoxy-3-methyl-α-D-xylofuranoside (0.74 g, 0.0028 mol) in dry pyridine (23 ml) was treated with benzoyl chloride (0.8 ml, 0.0056 mol). After being stirred overnight at room temperature, the solution was poured into ice water and the product was extracted into chloroform. Drying and evaporation left an oil which was purified by column chromatography (silica gel, 39:1 C_6H_6-EtOAc) to obtain a colorless product (0.95 g, 91% yield); R_f 0.42 (silica gel, 19:1 C_6H_6-EtOAc); nmr: τ ($CDCl_3$) 8.8 (d, J = 7.0 Hz, C_3-Me), 6.9 - 7.4 (m, C_3-H), 6.7 (s, OMe), 5.3 - 6.0 (complex m, C_4-H and C_5- H), 4.9 - 5.2 (dd, C_2-H), 4.56 (d, J = 4.0 Hz, C_1- H), 1.8 - 2.7 (complex m, aromatic protons).

Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.30; H, 5.84.

EXPERIMENTAL REPORT FORM

Compound(s):

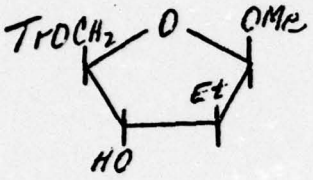


Name: Methyl 3-deoxy-3-ethyl-5-O-trityl-β-D-xylofuranoside

Code number: AM 349

Empirical formula: $C_{27}H_{30}O_4$

Molecular weight: 418.57



Name: Methyl 2-deoxy-2-ethyl-5-O-trityl-β-D-arabinofuranoside

Code number: AM 350

Empirical formula: $C_{27}H_{30}O_4$

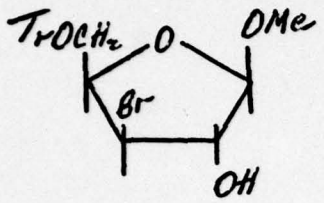
Molecular weight: 418.57

Procedure:

A stirred solution of methyl 2,3-anhydro-5-O-trityl-β-D-ribofuranoside (4.0 g, 0.010 mol) in ether (200 ml) was treated dropwise with 3M ethylmagnesium chloride in ether (17 ml, 0.05 mol), and the mixture was refluxed for 45 hr and poured into aqueous ammonium chloride, ether, and ice. The aqueous layer was separated and extracted four times with ether, and the combined ether layers were washed successively with aqueous ammonium chloride, saturated sodium bicarbonate, and water. Drying and evaporation left an oil which was chromatographed (silica gel, 49:1 to 19:1 C_6H_6-EtOAc) to give the following fractions: 1) unreacted epoxide, 2.85 g (71% recovery); 2) 3-deoxy-3-ethyl compound, pink-yellow spot, 0.3 g (8.0% yield); 3) 2-deoxy-2-ethyl compound, maroon spot, 0.7 g (16% yield). The 3-deoxy-3-ethyl isomer showed τ ($CDCl_3$) 5.19 (d, J = 2.0 Hz, C_1-H), whereas the 2-deoxy-2-ethyl isomer showed τ($CDCl_3$) 5.18 (d, J = 4.5 Hz, C_1-H).

EXPERIMENTAL REPORT FORM

Compound(s):

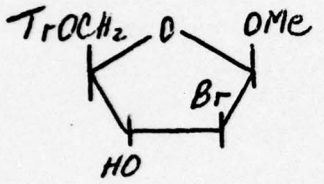


Name: Methyl 3-bromo-3-deoxy-5-O-trityl-β-D-xylofuranoside

Code number: AM 318

Empirical formula: $C_{25}H_{25}BrO_4$

Molecular weight: 469.38

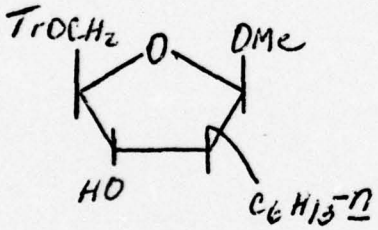


Name: Methyl 2-bromo-2-deoxy-5-O-trityl-β-D-arabinofuranoside

Code number: AM 332

Empirical formula: $C_{25}H_{25}BrO_4$

Molecular weight: 469.38

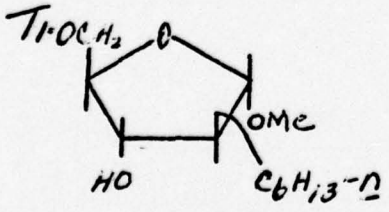


Name: Methyl 2-deoxy-2-n-hexyl-5-O-trityl-β-D-arabinofuranoside

Code number: AM 333

Empirical formula: $C_{31}H_{38}O_4$

Molecular weight: 474.65



Name: Methyl 2-deoxy-2-n-hexyl-5-O-trityl-α-D-arabinofuranoside

Code number: AM 351

Empirical formula: $C_{31}H_{38}O_4$

Molecular weight: 474.65

Procedure:

A stirred solution of methyl 2,3-anhydro-5-O-trityl-β-D-ribofuranoside (5.0 g, 0.013 mol)* in ether (200 ml) was treated dropwise with 3 M n-hexylmagnesium bromide (11 ml, 0.033 mol) in ether, and the mixture was refluxed for 2 days. Another portion (5 ml, 0.015 mol) of Grignard solution was added, and after a total of 1 week the reaction mixture was poured into a stirred mixture of ice water (200 ml), ammonium chloride (60 g), and ether (100 ml). The aqueous layer was separated and extracted with ether (4 x 150 ml). The combined ether layers were washed with 10% ammonium chloride, saturated aqueous sodium bicarbonate, and finally water. Drying and evaporation produced a syrup whose tlc (silic gel, 10:1 C_6H_6-EtOAc) showed spots at R_f 0.66 (blue-green, starting material), 0.64 (maroon, 2-deoxy-2-n-hexyl β-anomer), 0.54 (pinkish yellow; 2-bromo-2-deoxy compound), 0.46 (maroon, 2-deoxy-2-n-hexyl α-anomer), 0.37 (green, 3-bromo-3-deoxy compound, 0.23 (green), and 0.17 (yellow-green)(the latter 2 spots may be the α-anomers of the 3-bromo-3-deoxy and 2-bromo-2-deoxy compounds respectively). The crude product mixture was chromatographed on a silica gel column (49:1 to 19:1 C_6H_6-EtOAc) and the following fractions were isolated: 1) unchanged epoxide, 0.8 g (16% recovery); 2) mixture of 2-bromo-2-deoxy compound and 2-deoxy-2-n-hexyl α- and β-anomers, 1.1 g; 3) 3-bromo-3-deoxy compound, 2.8 g (46% yield). Fraction 2 was purified further by preparative tlc (silica gel, 20:1 C_6H_6-EtOAc) to give methyl 2-deoxy-2-n-hexyl-5-O-trityl-β-D-arabinofuranoside (0.55 g, 9% yield), methyl 2-bromo-2-deoxy-5-O-trityl-β-D-arabinofuranoside (0.30 g, 5% yield), and methyl 2-deoxy-2-n-hexyl-5-O-trityl-α-D-arabinofuranoside (0.12 g, 2% yield). The 3-bromo-3-deoxy compound showed the following nmr signals: τ ($CDCl_3$) 6.5 - 6.7 (singlet overlapping a multiplet, MeO and C_5-H), 5.4 - 6.0 (complex multiplet, C_2-H, C_3-H, and C_4-H), 5.15 (d, J $\leq$ 2 Hz, C_1-H), 2.4 - 2.9 (m, aromatic protons). The 2-bromo-2-deoxy compound showed the

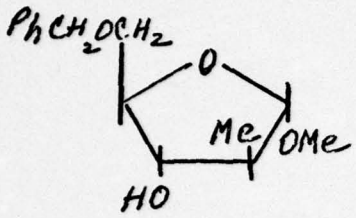
*The compound used in this reaction was judged to be quite pure on the basis of the nmr spectrum, but the possibility of minor contamination (<5%) by α-anomer could not be ruled out.

following nmr signals: τ ($CDCl_3$) 6.5 - 6.7 (m, C_5-H), 6.6 (s, MeO), 5.4 - 6.1 (complex, m, C_2-H, C_3-H, and C_4-H), 5.16 (d, J = 4.0 Hz, C_1-H), 2.3 - 2.8 (m, aromatic protons). The 2-deoxy-2-n-hexyl β-anomer showed the following nmr signals: τ ($CDCl_3$) 8.3 - 9.0 (m, n-hexyl protons), 7.7 - 8.1 (broad m, C_2-H), 6.6 - 6.8 (m, C_5-H), 6.7 (s, MeO), 6.0 - 6.3 (broad m, C_3-H and C_4-H), 5.18 (d, J = 4.5 Hz, C_1-H), 2.3 2.8 (m, aromatic protons). The 2-deoxy-2-n-hexyl α-anomer showed the following nmr signals: τ ($CDCl_3$) 8.3 - 9.2 (m, n-hexyl protons), 7.6 - 7.8 (broad m, C_2-H), 6.5 - 6.8 (m, C_5-H), 6.6 (s, MeO), 5.8 - 6.4 (m, C_3-H and C_4-H), 5.30 (d, J $\leq$ 2 Hz, C_1-H), 2.4 - 2.8 (m, aromatic protons). The 3-bromo-3-deoxy compound was obtained as a solid, and could be recrystallized from a mixture of ether and petroleum ether; mp 155 - 156°. The 2-deoxy-2-n-hexyl β-anomer was sent for microanalysis.

Calcd. for $C_{31}H_{38}O_4 \cdot 0.5\ H_2O$: C, 76.98; H, 8.12. Found: C, 76.81; H, 7.77.

EXPERIMENTAL REPORT FORM

Compound:

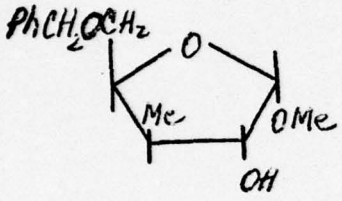


Name: Methyl 5-O-benzyl-2-deoxy-2-methyl-α-D-arabinofuranoside

Code number: AM 347

Empirical formula: $C_{14}H_{20}O_4$

Molecular weight: 252.34



Name: Methyl 5-O-benzyl-3-deoxy-3-methyl-α-D-xylofuranoside

Code number: AM 349

Empirical formula: $C_{14}H_{20}O_4$

Molecular weight: 252.34

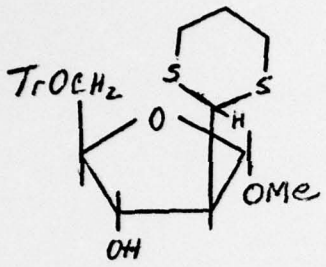
Procedure:

A stirred solution of methyl 2,3-anhydro-5-O-benzyl-α-D-ribofuranoside (2.0 g, 0.0085 mol) in dry ether (100 ml) was treated dropwise with 3.2 M methylmagnesium chloride in tetrahydrofuran (20 ml, 0.064 mol). The mixture was stirred for 3 days at room temperature, then refluxed 6 hr under a nitrogen atmosphere, cooled, and poured into an ice-cold mixture of aqueous ammonium chloride and ether. The organic layer was separated, the aqueous layer was extracted repeatedly with ether, and the combined extracts were washed successively with 10% ammonium chloride, saturated sodium bicarbonate, and water. Drying and solvent removal left an oil which was purified by column chromatography (silica gel, ether - petr. ether). Three fractions were obtained: 1) mixture of 2-chloro and 3-chloro compounds, 1.4 g (60% yield); 2) methyl 5-O-benzyl-3-deoxy-3-methyl-α-D-xylofuranoside, 0.15 g (7% yield); 3) methyl 5-O-benzyl-2-deoxy-2-methyl-α-D-arabinofuranoside, 0.3 g (14% yield). The

3-deoxy-3-methyl compound gave the following nmr signals: τ ($CDCl_3$) 8.70 (d, J = 7.0 Hz, C_3-Me), 5.18 (d, J = 4.5 Hz, C_1-H). The 2-deoxy-2-methyl compound gave the following nmr signals: τ ($CDCl_3$) 8.60 (d, J = 7.5 Hz, C_2-Me), 5.36 (d, $J \leq 2$ Hz, C_1-H).

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2-deoxy-2-(1',3-dithian-2'-yl)-5-O-trityl-α-D-arabinofuranoside

Code Number: AM 319

Empirical formula: $C_{29}H_{32}O_4S_2$

Molecular weight: 508.63

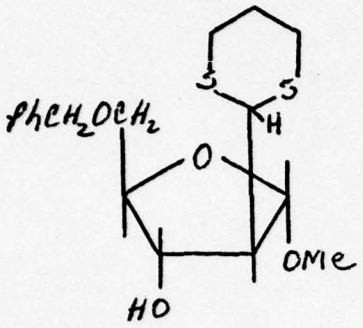
Procedure:

n-Butyl lithium (17.8 ml of 2.3 M solution in hexane, 0.04 mole) was added with stirring, under a nitrogen atmosphere, to a solution of 1,3-dithiane (4.8 g, 0.04 mole) in dry tetrahydrofuran (50 ml) at -40° (bath temperature), and stirring was continued at -30° to -20° for 2.5 hr. A solution of methyl 2,3-anhydro-5-O-trityl-α-D-ribofuranoside (1.94 g, 0.005 mole) in dry tetrahydrofuran (50 ml) was added dropwise with continued cooling (-40°) and after 2 hr at -30° to -20° the mixture was left to stir at 0° under nitrogen for 4 days, at which time tlc analysis showed complete absence of starting material. The reaction mixture was poured into ice water (200 ml), the product was extracted with ether (4 x 75 ml), and the combined ether extracts were washed with saturated sodium chloride (2 x 75 ml), dried and evaporated. Chromatography of the oily residue on silica gel with 19:1 benzene-ethyl acetate gave an oily solid (2.1 g, 86%); ir (KCl) ν 3450 cm^{-1} (OH); nmr ($CDCl_3$) τ 7.8 - 8.2 (m, SCH_2CH_2), 7.0 - 7.4 (m, SCH_2CH_2), 6.6 (s, MeO), 6.4 - 6,6 (m, C_5-H), 6.1 (s, SCHS), 5.8 - 6.0 (m, C_2-H, C_3-H, and C_4-H), 4.98 (d, J = 1.5 Hz, C_1-H), 2.2 - 3.0 (m, aromatic protons).

Calcd. for $C_{29}H_{32}O_4S_2$: C, 68.47; H, 6.34; Found: C, 68.46; H, 6.28.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 5-O-benzyl-2-deoxy-2-(1',3'-dithian-2'-yl)-α-D-arabinofuranoside

Code number: AM 325

Empirical formula: $C_{17}H_{24}O_4S_2$

Molecular weight: 356.43

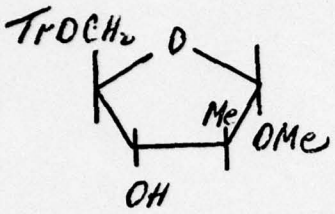
Procedure:

Methyl 2,3-anhydro-5-O-benzyl-α-D-ribofuranoside (1.2 g, 0.005 mole) was allowed to react with 1,3-dithian-2-yl lithium (0.04 mole) in dry tetrahydrofuran for 3 hr at -30° to -20° and then for 3 days at 0°. Column chromatography on silica gel with mixtures of petroleum ether (bp 30 - 60°) and ether gave a yellow oil (1.55 g, 87%); ir (thin film) ν 3500 cm^{-1} (OH); nmr ($CDCl_3$) τ 7.8 - 8.2 (m, $SCH_2\underline{CH_2}$), 7.0 - 7.4 (m, $SC\underline{H_2}CH_2$), 6.6 (s, MeO), 6.2 - 6.4 (m, C_5-H), 6.1 (s, SCHS), 5.7 - 5.9 (m, C_2-H, C_3-H, and C_4-H), 5.4 (s, $PhC\underline{H_2}$), 4.98 (d, J = 1.5 Hz, C_1-H), 2.6 (aromatic protons).

Calcd. for $C_{17}H_{24}O_4S_2$: C, 57.27; H, 6.79; S, 17.99. Found: C, 57.35; H, 6.84; S, 17.85.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2-deoxy-2-methyl-5-O-trityl-α-D-arabinofuranoside

Code number: AM 320

Empirical formula: $C_{26}H_{28}O_4$

Molecular weight: 404.54

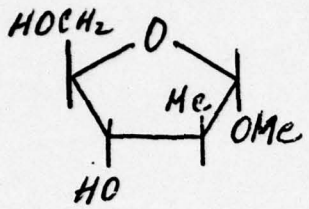
Procedure:

A mixture of methyl 2-deoxy-2-(1',3'-dithian-2'-yl)-5-O-trityl-α-D-arabinofuranoside (1.6 g, 0.0032 mol) and Davison sponge nickel (45 g) in absolute ethanol (450 ml) was stirred under reflux for 4 hr, cooled to room temperature, and filtered. The filter cake was washed repeatedly with ethanol, and the combined filtrate and wash solutions were evaporated under reduced pressure. The residue was dissolved in chloroform (300 ml), and a small amount of insoluble material was filtered off. Evaporation of the chloroform extract and chromatogrpahy of the oily residue on silica gel with 10:1 benzene-ethyl acetate gave a colorless glass (1.2 g, 95%); R_f 0.38 (9:1 benzene-ethyl acetate); nmr ($CDCl_3$) τ 9.0 (d, J = 7.5 Hz, C_2-Me), 7.8 - 8.0 (m, C_2-H), 6.4 - 7.0 (complex m, C_5-H), 6.6 (s, MeO), 5.8 - 6.1 (m, C_3-H and C_4-H), 5.42 (d, J = 1.5 Hz, C_1-H), 2.4 - 2.9 (m, aromatic protons).

Calcd. for $C_{26}H_{28}O_4$: C, 77.20; H, 6.88; Found: C, 77.15; H, 6.88.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 2-deoxy-2-methyl-α-D-arabinofuranoside

Code number: AM 323

Empirical formula: $C_7H_{14}O_4$

Molecular weight: 162.21

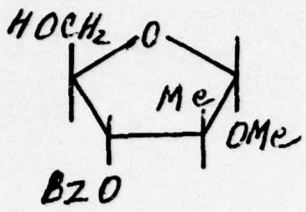
Procedure:

Treatment of methyl 5-O-benzyl-2-deoxy-2-(1',3'-dithian-2'-yl)-α-D-arabinofuranoside (0.7 g, 0.002 mole) directly with Davison sponge nickel in boiling ethanol for 5 hr gave a colorless oil (0.25 g, 77%) whose properties were consistent with simultaneous dethiation and de-O-benzylation; R_f 0.42 (ethyl acetate, spot visualized by exposure to iodine vapor); nmr ($CDCl_3$) τ 8.9 (d, J = 7.5 Hz, C_2-Me), 7.8 - 8.0 (broad m, C_2-H), 6.6 (s, MeO), 5.8 - 6.4 (broad m, C_3-H, C_4-H, and C_5-H), 5.38 (d, J = 1.5 Hz, C_1-H).

Calcd. for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.88; H, 8.68.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 3-O-benzoyl-2-deoxy-2-methyl-α-D-arabinofuranoside

Code number: AM 322

Empirical formula: $C_{14}H_{18}O_5$

Molecular weight: 266.32

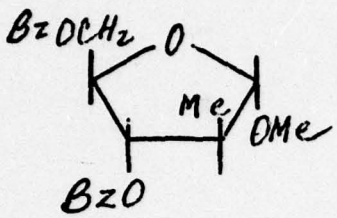
Procedure:

Methyl 3-O-benzoyl-2-deoxy-2-methyl-5-O-trityl-α-D-arabinofuranoside (5 g, 0.01 mole) in acetic acid (35 ml), water (25 ml), and methanol (20 ml) was stirred under reflux for 16 hr, cooled, and evaporated to dryness under reduced pressure. Removal of all the acetic acid by repeated azeotropic distillation with methanol, and chromatography on silica gel (120 g) with 19:1 benzene-ethyl acetate as the eluent gave a colorless oil (2 g, 76%); R_f 0.28 (4:1 benzene-ethyl acetate; ir (thin film) τ 1725 cm^{-1} (C=O); nmr ($CDCl_3$) τ 8.8 (d, J = 7.5 Hz, C_2-Me), 7.3 - 7.7 (m, C_2-H), 6.6 (s, MeO), 5.9 - 6.1 (broad s, C_5-H), 5.5 - 5.9 (m, C_4-H), 5.25 (d, J = 1.5 Hz, C_1-H), 4.9 - 5.1 (m, C_3-H), 1.8 - 2.7 (complex m, aromatic protons).

Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.33; H, 6.96.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 3,5-di-O-benzoyl-2-deoxy-2-methyl-α-D-arabinofuranoside

Code number : AM 324

Empirical formula: $C_{21}H_{22}O_6$

Molecular weight: 370.43

Procedure:

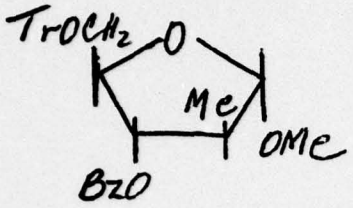
Method A. A solution of methyl 3-O-benzoyl-2-deoxy-2-methyl-α-D-arabinofuranoside (2 g, 0.0075 mole) in dry pyridine (60 ml) was treated with benzoyl chloride (2 ml), the mixture was stirred at room temperature overnight and poured into ice water, and the product was extracted with several portions of chloroform and worked up in the usual way. After chromatography on silica gel (80 g) with 39:1 benzene-ethyl acetate as the eluent, the diester was isolated as a colorless oil (2.8 g, 100%); R_f 0.46 (19:1 benzene-ethyl acetate); ir (thin film) ν 1725 cm^{-1} (C=O); nmr ($CDCl_3$) τ 8.8 (d, J = 7.5 Hz, C_2-Me), 7.4 - 7.8 (m, C_2-H), 6.6 (s, MeO), 5.2 - 5.6 (complex m, C_4-H and C_5-H), 5.19 (d, J = 1.5 Hz, C_1-H), 4.9 - 5.1 (m, C_3-H), 1.8 - 2.8 (complex m, aromatic protons).

Calcd. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.01; H, 5.96.

Method B. Benzoyl chloride (1 ml) was added dropwise with stirring to a solution of diol in dry pyridine (30 ml), and after overnight stirring at room temperature the mixture was worked up in the usual way. Chromatography on silica gel with 39:1 benzene-ethyl acetate as the eluent gave a colorless oil (0.5 g, 96%) whose ir and nmr spectra were indistinguishable from those of the product obtained by Method A.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 3-O-benzoyl-2-methyl-5-O-trityl-$_{\alpha}$-D-arabino=furanoside

Code number: AM 321

Empirical formula: $C_{32}H_{32}O_5$

Molecular weight: 496.64

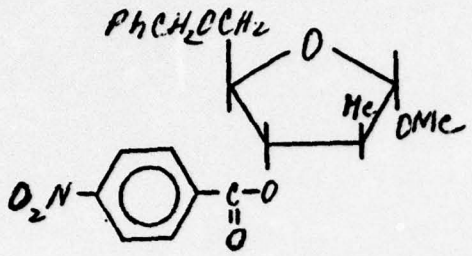
Procedure:

Methyl 2-deoxy-2-methyl-5-O-trityl-α-D-arabinofuranoside (4.1 g, 0.01 mole) was dissolved in dry pyridine (82 ml), benzoyl chloride (2.6 ml) was added dropwise with stirring, and the mixture was stirred at room temperature overnight. A few drops of water were added to dissolve the dense precipitate of pyridine hydrochloride, the solution was poured into ice water (150 ml), and the product was extracted with three portions of chloroform. The combined organic layers were washed successively with water, cold 4% hydrochlorid acid, and saturated sodium bicarbonate, rinsed again with water, dried, and evaporated to a syrup. Removal of the last traces of pyridine via repeated azeotropic distillation with toluene gave an amber-colored glass (5 g, 97%); R_f 0.42 (40:1 benzene-ethyl acetate); ir (thin film) ν 1725 cm^{-1} (C=O).

Calcd. for $C_{32}H_{32}O_5$: C, 77.93; H, 6.34. Found: C, 77.72; H, 6.38.

EXPERIMENTAL REPORT FORM

Compound:



Name: Methyl 5-O-benzyl-2-deoxy-2-methyl-3-O-p-nitrobenzoyl-α-D-arabinofuranoside

Code number: AM 348

Empirical formula: $C_{21}H_{23}NO_7$

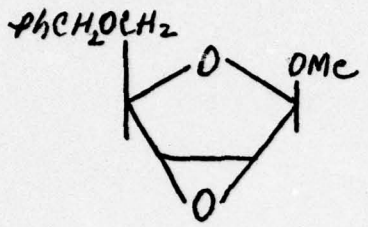
Molecular weight: 401.45

Procedure:

A stirred solution of methyl 5-O-benzyl-2-deoxy-2-methyl-α-D-arabinofuranoside (1.26 g, 0.005 mol) in dry pyridine (50 ml) was treated with p-nitrobenzoyl chloride (1.7 g, 0.0093 mol) at room temperature overnight. Water (5 ml) was added and stirring allowed to continue for another hr, whereupon pyridine and water were evaporated under reduced pressure and the residue was extracted with chloroform. The extract was washed with 5% hydrochloric acid (3 x 25 ml), saturated sodium bicarbonate, and finally water. Evaporation of the chloroform and column chromatography (silica gel, 50:1 C_6H_6-EtOAc) gave 1.35 g (54% yield) of product as an oil; nmr: τ ($CDCl_3$) 8.72 (d, J = 7.5 Hz, C_2-Me), 7.4 - 7.8 (m, C_2-H), 6.5 (s, MeO), 6.2 (broad d, C_5-H), 5.4 - 5.8 (m, C_4-H), 5.3 (s, $PhCH_2$), 5.16 (d, J ≤ 2 Hz, C_1-H), 4.8 - 5.0 (o, C_3-H), 1.7 and 2.6 (singlets, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound:

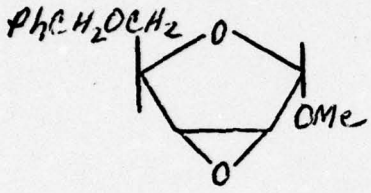


Name: Methyl 2,3-anhydro-5-O-benzyl-β-D-ribofuranoside

Code number: AM 314

Empirical formula: $C_{13}H_{16}O_4$

Molecular weight: 236.29



Name: Methyl 2,3-anhydro-5-O-benzyl-α-D-ribofuranoside

Code number: AM 315

Empirical formula: $C_{13}H_{16}O_4$

Molecular weight: 236.29

Procedure:

A solution of 5-O-benzyl-1,2-O-isopropylidene-D-xylofuranose (16.8 g, 0.06 mol) and p-toluenesulfonyl chloride (15 g, 0.079 mole) in pyridine (102 ml) was heated at 60-70° for 6 hr in a flask protected from moisture. The mixture was cooled and poured into ice water (500 ml), and the product was extracted with chloroform (4 x 100 ml). The combined organic layers were washed with ice-cold 1% sulfuric acid, rinsed to neutrality with water, dried and evaporated to a brown syrup (20 g, 87%). A solution of this material (50 g, 0.15 mole) in 1% methanolic hydrogen chloride (1200 ml) was refluxed for 5 hr, cooled, neutralized carefully with sodium bicarbonate, filtered, and evaporated under reduced pressure. The residue was taken up in water and the solution extracted with chloroform (4 x 90 ml). The combined extracts were dried over anhydrous magnesium sulfate and evaporated to a brown syrup (44 g, 82%) consisting of a mixture of methyl 5-O-benzyl-3-tosyl-α-

D-xylofuranoside and methyl 5-O-benzyl-3-O-tosyl-β-D-xylofuranoside. This mixture (44 g, 0.11 mole) was dissolved directly in dry methanol (67 ml), to which was then added an ice-cold solution of sodium methoxide (6.4 g, 0.12 mole) in methanol (56 ml). After 4 days in a stoppered flask at about 5° the mixture was treated with Celite (5 g) and filtered, the filter cake was washed with methanol, and the combined filtrate and washings were neutralized with glacial acetic acid and evaporated under reduced pressure. The residue was taken up in water and the solution extracted with chloroform (4 x 90 ml). The combined extracts were dried and evaporated, and the residue was chromatographed on a silica gel column with mixtures of petroleum ether (bp 30-60°) and ether ranging in composition from 9:1 to 8:2. The separation of anomeric epoxides was monitored by tlc (silica gel, 19:6 petroleum ether-ether). The faster-moving product (10.9 g, 43%) was methyl 2,3-anhydro-5-O-benzyl-β-D-ribofuranoside; R_f 0.33; nmr: τ ($CDCl_3$) 6.7 (s, MeO), 6.2 - 6.5 (complex m, C_3-H, C_4-H, and C_5-H), 5.7 (dd, C_2-H), 5.5 (d, $PhCH_2$), 5.13 (s, C_1-H), 2.7 (s, aromatic protons).*

Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.92; H, 6.86.

The slower component (6.3 g, 25%) was methyl 2,3-anhydro-5-O-benzyl-α-D-ribofuranoside; R_f 0.14; nmr: τ ($CDCl_3$) 6.5 (s, MeO), 6.2 - 6.6 (complex m, C_3-H, C_4-H, and C_5-H), 5.6 (t, J = 3.0 Hz, C_2-H), 5.5 (s, $PhCH_2$), 4.86 (s, C_1-H), 2.7 (s, aromatic protons).**

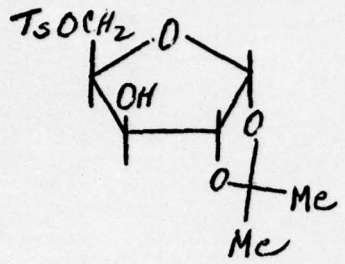
Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.83; H, 6.79.

* J. A. Wright and N. F. Taylor, Carbohyd. Res., 6, 347 (1968).

** J. A. Wright, N. F. Taylor, and J. J. Fox, J. Org. Chem., 34, 2632 (1969).

EXPERIMENTAL REPORT FORM

Compound:



Name: 1,2-O-Isopropylidene-5-O-tosyl-D-xylofuranose

Code number: AM 300

Empirical formula: $C_{15}H_{20}O_7S$

Molecular weight: 344.36

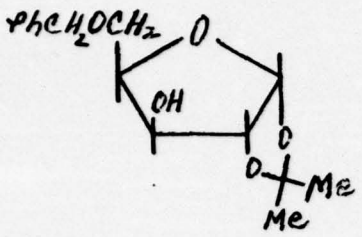
Procedure:

To a stirred solution of 1,2-O-isopropylidene-D-xylofuranose (36 g, 0.188 mol) in dry pyridine (180 ml) was added dropwise with cooling in ice a solution of p-toluenesulfonyl chloride (40 g, 0.21 mol) in chloroform (100 ml). After 1 hr at 0° the mixture was left at room temperature overnight, water (30 ml) was added, the mixture was stirred for 30 min, a large volume of water was added, and the product was extracted with chloroform. The combined extracts were washed with ice-cold 5% sulfuric acid until the pH of the aqueous layer was faintly acidic, then rinsed (3x) with water, dried, and concentrated under reduced pressure. The syrupy residue crystallized spontaneously to give 63 g (96% yield) of product; mp 130-133° (lit.* 133-134°).

* P. A. Levene and A. L. Raymond, J. Biol. Chem., 102, 317 (1933).

EXPERIMENTAL REPORT FORM

Compound:



Name: 5-O-Benzyl-1,2-O-isopropylidene-D-xylofuranose

Code number: AM 301

Empirical formula: $C_{15}H_{20}O_5$

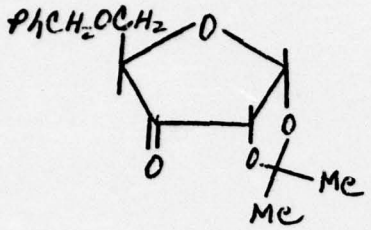
Molecular weight: 280.35

Procedure:

Sodium metal (18.4 g, 0.8 mol) was added to benzyl alcohol (300 ml) and the mixture was heated and stirred until all the sodium dissolved. After addition of 1,2-O-isopropylidene-5-O-tosyl-D-xylofuranose (from 36 g, 0.188 mol) of 1,2-O-isopropylidene-D-xylofuranose), the mixture was heated at 100-110° for 20 hr, diluted with water and neutralized with acetic acid. Enough water was added to dissolve all the precipitated solids, and the product was extracted into chloroform. Washing, drying, and evaporation under reduced pressure gave a brown syrup. Vacuum distillation produced a colorless liquid, bp 150-155° (0.07 mm), which solidified in the receiver. The colorless solid weighed 34.4 g (65% yield starting from 1,2-O-isopropylidene-D-xylofuranose); mp 60-63°; nmr: τ ($CDCl_3$) 8.71 and 8.55 (singlets, $Me_2\overset{|}{C}$-), 6.0 - 6.2 (m, C_5-H), 5.6 - 5.85 (m, C_3-H and C_4-H), 5.5 (d, J = 4 Hz, C_2-H), 5.4 (s, $PhC\underline{H}_2$), 4.30 (d, J = 4 Hz; C_1-H), 2.7 (s, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound(s):

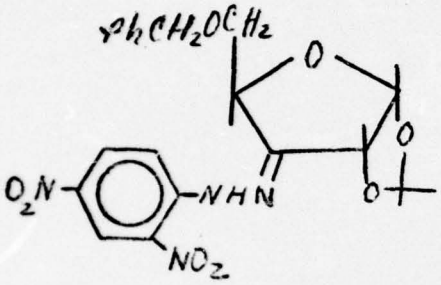


Name: 5-O-Benzyl-1,2-O-isopropylidene-D-erythropentos-3-ulose

Code number: AM 329

Empirical formula: $C_{15}H_{18}O_5$

Molecular weight: 278.33



Name: 5-O-Benzyl-1,2-O-isopropylidene-D-erythropentos-3-ulose 2,4-dinitrophenylhydrazone

Code number: AM 330

Empirical formula: $C_{21}H_{22}N_4O_8$

Molecular weight: 458.47

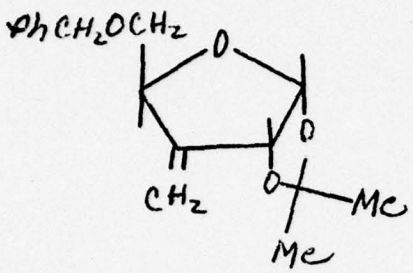
Procedure:

A solution of 5-O-benzyl-1,2-O-isopropylidene-D-xylofuranose (5.2 g, 0.019 mol) in DMSO (60 ml) and acetic anhydride (40 ml) was kept at room temperatuere for 24 hr. Water (10 ml) was then added and the solution concentrated to dryness under reduced pressure. The residue was diluted with water and the product extracted into several portions of chloroform which were combined, washed with water, dried, and evaporated to give the ketone as a syrup (5.2 g, 100% yield); infrared: $\nu_{C=O}$ 1795 cm $^{-1}$; nmr: τ ($CDCl_3$) 8.61 and 8.58 (singlets, $Me_2\dot{C}$-), 6.4 (d, C_5-H), 5.3 - 5.8 (complex m, C_2-H, C_4-H, and $PhC\underline{H}_2$), 3.90 (d, J = 4.5 Hz, C_1-H), 2.7 (s, aromatic protons). The 2,4-dinotrophenylhydrazone derivative was prepared in the standard manner; mp 146-147° (EtOH) (lit.* 143-144°).

* A. Rosenthal and D. A. Baker, Tetrahedron Letters, 397 (1967).

EXPERIMENTAL REPORT FORM

Compound:



Name: 5-O-Benzyl-3-deoxy-1,2-O-isopropylidene-3-methylene-D-ribofuranose

Code number: AM 349

Empirical formula: $C_{16}H_{20}O_4$

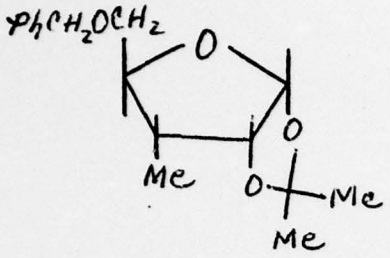
Molecular weight: 276.36

Procedure:

To a stirred solution of 2 N n-butyl lithium in ether under a nitrogen atmosphere (11 ml) was added methyl triphenylphosphonium bromide (7.15 g, 0.02 mol). The mixture was stirred at room temperature for 3 hr, and the resulting orange solution of triphenylphosphine methylene was added dropwise to a stirred solution of 5-O-benzyl-1,2-O-isopropylidene-D-erythropentos-3-ulose (5.6 g, 0.02 mol) in ether (30 ml) under nitrogen. After 2 hr at room temperature and 4 hr under reflux the cooled solution was poured into ice water (50 ml), the ether layer was separated, the aqueous layer was extracted several times with ether, and the combined ether layers were washed (3x) with saturated sodium chloride, dried, and evaporated. The residue was purified on a column (silica gel, 10:1 petr. ether-ether) to give a colorless syrup (2.9 g, 53%); R_f 0.55 (silica gel, 10:1 C_6H_6-EtOAc); nmr: τ ($CDCl_3$) 8.62 and 8.47 (singlets, $Me_2\dot{C}$-), 6.4 - 6.6 (m, C_5-H), 5.5 (s, $PhC\underline{H}_2$), 5.1 - 5.3 (m, C_2-H and C_4-H), 4.6 and 4.9 (doublet of triplets, $=CH_2$), 4.24 (d, J = 8 Hz, C_1-H), 2.8 (s, aromatic protons).

EXPERIMENTAL REPORT FORM

Compound:



Name: 5-O-Benzyl-3-deoxy-1,2-O-isopropylidene-3-methyl-α-D-xylofuranose

Code number: AM 331

Empirical formula: $C_{16}H_{22}O_4$

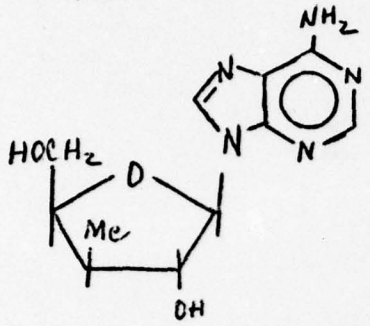
Molecular weight: 278.38

Procedure:

A solution of 5-O-benzyl-1,2-O-isopropylidene-3-methylene-α-D-ribofuranose in ethanol was shaken in a Parr hydrogenation apparatus in the presence of 10% palladium on carbon. The catalyst was filtered off and the solvent evaporated under reduced pressure to give a pale yellow oil.

EXPERIMENTAL REPORT FORM

Compound:



Name: 9-(2-Deoxy-2-methyl-β-D-xylofuranosyl)adenine

Code number: NU 211

Empirical formula: $C_{11}H_{15}N_5O_3$

Molecular weight: 265.31

Procedure:

Method A. A mixture of acetyl chloride (5 ml) and glacial acetic acid (50 ml) pre-saturated at <10° with dry HCl gas was added at 10° to a solution of methyl 5-O-benzoyl-3-deoxy-3-methyl-β-D xylofuranoside (2.0 g, 0.0054 mol) in glacial acetic acid (25 ml). The solution was kept in a stoppered flask at room temperature for 4 hr and then evaporated to dryness under reduced pressure (both temperatures below 40°). Four 25 ml portions of dry toluene were added and removed by vacuum distillation, and the residue was dissolved in ether (100 ml) that had been pre-saturated with dry HCl gas at 0° and contained acetyl chloride (5 ml). After 3 days at 0° in a stoppered flask, the solution was evaporated under reduced pressure (bath temp. < 40°) and the residue was dried by azeotropic vacuum distillation of toluene (4 x 25 ml). The resulting chloro sugar (2.0 g, ca. 100% yield) was a dark brown syrup.

Xylene (ca. 150 ml) was distilled from a suspension of chloromercuri-6-benzamidopurine (3.4 g) and Celite (2 g) in xylene (250 ml). The mixture was cooled to room temperature, treated with a solution of chloro sugar (2.0 g, 0.0054 mol) in dry xylene (50 ml), and stirred under reflux for 4 hr. The hot mixture was filtered, and the filtrate was diluted with petroleum ether (300 ml) and kept at 0° overnight. The precipitate was collected and dissolved in chloroform (400 ml),

and the solution was washed with 30% potassium iodide (3 x 80 ml), dried, and evaporated. The residue (2.8 g) was dissolved in 0.05 sodium methoxide in methanol (140 ml) and the solution refluxed for 4 hr. Cooling, neutralization with acetic acid, evaporation, and preparative tlc (silica gel plates, 4:9:2 C_6H_6-EtOAc-MeOH) gave 0.68 g (48% yield) of colorless product; mp 186 - 187.5° (MeOH-Et_2O); R_f 0.40 (silica gel, 1:3:1 C_6H_6-EtOAc-MeOH), 0.76 (silica gel, 6:4:1 $CHCl_3$-MeOH-H_2O); ir: ν (KCl) 3300-3200 (NH and OH), 1670 (NH_2) cm^{-1}; nmr: τ (d_6-DMSO) 8.84 (d, J = 7.0 Hz, $C_{3'}$-Me), 6.7 (d, J = $C_{3'}$-H), 6.2 (broad s, $C_{5'}$-H), 5.2 - 5.8 (complex m, $C_{2'}$-H and $C_{4'}$-H), 4.28 (d, J = 7.0 Hz, $C_{1'}$-H), 2.6 (s, NH_2), 1.8 (s, C_8-H), 1.6 (s, C_2-H). Traces of α-anomer were detected in the tlc of the crude product prior to purification.

Method B. A mixture of acetyl chloride (2 ml) and glacial acetic acid (12 ml) pre-saturated at <10° with dry HCl gas was added at 10° to a solution of methyl 5-O-benzoyl-3-deoxy-3-methyl-α-D-xylofuranoside (0.9 g, 0.0024 mol) in glacial acetic acid (12 ml). The solution was kept in a stoppered flask at room temperature for 4 hr and then evaporated to dryness under reduced pressure (bath temp. < 40°). Four 20 ml portions of toluene were added and removed by vacuum distillation, and the brown syrupy residue was dissolved in ether (50 ml) which had been pre-saturated with dry HCl gas at 0° and contained acetyl chloride (2 ml). After 3 hr at room temperature in a stoppered flask the solution was evaporated under reduced pressure (bath temp. < 40°) and the residue was dried by azeotropic vacuum distillation of toluene (4 x 20 ml). The resulting chloro sugar (0.9 g) was a dark brown syrup.

Xylene (ca. 120 ml) was distilled from a suspension of chloromercuri-6-benzamidopurine (1.7 g) and Celite (1 g) in dry xylene (200 ml). The mixture was cooled to room temperature, treated with a solution of chloro sugar (0.9 g, 0.0026 mol) in dry xylene (25 ml), and stirred under reflux for 4 hr. The hot mixture was filtered, and the filtrate was evaporated under reduced pressure. Extraction of the residue with chloroform (300 ml) left a small amount of insoluble material which was filtered off. The chloroform extract was washed with 30% potassium iodide (3 x 50 ml) and

then water. Drying and solvent evaporation gave a solid (1.3 g) which was dissolved directly in 0.05 N sodium methoxide in methanol and heated under reflux for 4 hr. Cooling, neutralization with acetic acid, evaporation, and preparative tlc (silica gel plates, 1:3:1 C_6H_6-EtOAc-MeOH) gave 0.37 g (57% yield) of colorless product whose R_f values and spectral properties were identical with the material obtained with Method A.

Calcd. for $C_{11}H_{15}N_5O_3 \cdot 0.5\ H_2O$: C, 48.17; H, 5.88; N, 25.54. Found: C, 48.38; H, 5.70; N, 25.48.

B. Compounds Submitted for Antimalarial Evaluation (1 June 74 to 30 June 76)

During the period covered by this report and the preceding contract year (cf. Annual Report, 1 June 74 - 31 May 75, pp 53 - 54), the following samples were submitted for testing:

Compound Name	SFCC and WRAIR Numbers *	Weight in grams
1,2-O-Isopropylidene-5-O-tosyl-D-xylofuranose	AM 300 BE 19833	0.5
5-O-Benzyl-1,2-O-isopropylidene-D-xylofuranose	AM 301 BE 19842	0.5
5-O-Benzoyl-1,2-O-isopropylidene-D-erythropentos-3-ulofuranose	AM 302 BE 19851	0.5
5-O-Ethoxycarbonyl-1,2-O-isopropylidene-D-xylofuranose	AM 303 BE 58474	0.5
5-O-Ethoxycarbonyl-1,2-O-isopropylidene-3-O-tosyl-D-xylofuranose	AM 304 BE 58483	0.5
1,2-O-Isopropylidene-5-O-methoxycarbonyl-D-xylofuranose	AM 305 BE 58492	0.5
1,2-O-Isopropylidene-5-O-mesyl-5-O-methoxycarbonyl-D-xylofuranose	AM 306 BE 58509	0.5
1,2-Di-O-acetyl-5-O-benzoyl-3-deoxy-3-methyl-(α,β)-D-ribofuranose	AM 307 BE 58518	0.5 0.15
1,2-Di-O-acetyl-5-O-benzoyl-3-deoxy-3-n-hexyl-(α,β)-D-ribofuranose	AM 308 BE 58527	0.5
Methyl 2,3-anhydro-5-O-trityl-α-D-ribofuranoside	AM 309 BE 76105	0.5
Methyl 2,3-anhydro-5-O-trityl-β-D-ribofuranoside	AM 310 BE 76114	0.5
Methyl 2,3-anhydro-β-D-ribofuranoside	AM 311 BG 44309	1.0
Methyl 3-chloro-3-deoxy-5-O-trityl-β-D-xylofuranoside	AM 312	1.0 0.32
Methyl 3-chloro-3-deoxy-5-O-trityl-α-D-xylofuranoside	AM 313 BG 44327	0.5 1.2
Methyl 2,3-anhydro-5-O-benzyl-β-D-ribofuranoside	AM 314 BG 44336	1.0

Compound Name	SFCC and WRAIR Numbers	Weight in grams
Methyl 2,3-anhydro-5-O-benzyl-α-D-ribofuranoside	AM 315 BG 44345	1.0
Methyl 5-O-benzyl-3-chloro-3-deoxy-α-D-xylofuranoside	AM 316 BG 44354	1.0
Methyl 2,3-anhydro-α-D-ribofuranoside	AM 317 BG 44363	1.0
Methyl 3-bromo-3-deoxy-5-O-trityl-β-D-xylofuranoside	AM 318 BG 48996	0.5 1.5
Methyl 3,5-di-O-benzoyl-2-deoxy-2-methyl-α-D-arabino-furanoside	AM 324	0.28
5-O-Benzyl-1,2-O-isopropylidene-D-erythropentos-3-ulofuranose	AM 329	0.30
5-O-Benzyl-1,2-O-isopropylidene-D-erythropentos-3-ulofuranose 2,4-dinitrophenylhydrazone	AM 330	0.40
5-O-Benzyl-3-deoxy-1,2-O-isopropylidene-3-methyl-D-ribofuranose	AM 331	0.22
Methyl 2-bromo-2-deoxy-5-O-trityl-β-D-arabinofuranoside	AM 332	0.50
1,2-O-Isopropylidene-5-O-methoxycarbonyl-3-O-tosyl-D-xylofuranose	AM 336	2.0
8-Bromoadenosine 3',5'-cyclic phosphate	NU 200 BE 19806	0.5
9-Bromo-2'-O-tosyladenosine 3',5'-cyclic phosphate	NU 201 BE 19815	0.5
8-Hydroxy-2'-O-tosyladenosine 3',5'-cyclic phosphate	NU 202 BE 19824	0.5
9-(3'-Deoxy-3'-methyl-β-D-ribofuranosyl)adenine	NU 206 BE 75984	1.3
9-(3'-Deoxy-3'-ethyl-β-D-ribofuranosyl)adenine	NU 207 BE 58956 BE 75993	0.1 1.0
9-(3'-n-Butyl-3'-deoxy-β-D-ribofuranosyl)adenine	NU 208 BE 58965 BE 76007	0.1 1.6
9-(3'-Deoxy-3'-n-hexyl-β-D-ribofuranosyl)adenine	NU 209 BE 76016	1.2
9-(3'-Deoxy-3'-methyl-β-D-xylofuranosyl)adenine	NU 211 BG 47159	0.5

* Samples for which only SFCC numbers are given have not been assigned WRAIR bottle numbers as of the date of this report.

IV. DISTRIBUTION LIST

4 copies	HQDA (SGRD-RP) Washington, D. C. 20314
12 copies	Defense Documentation Center (DDC) ATTN: DDC-TCA Cameron Station Alexandria, Virginia 22314
1 copy	Superintendent Academy of Health Sciences, U. S. Army ATTN: AHS-COM Fort Sam Houston, Texas 78234
16 copies	Director Walter Reed Army Institute of Research ATTN: Division of Medicinal Chemistry Washington, D. C. 20012
1 copy	Dean School of Medicine Uniformed Services University of the Health Sciences Office of the Secretary of Defense 6917 Arlington Road Bethesda, MD 20014